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(12) # DEMANDE DE BREVET D'INVENTION **A1**

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(71) **Demandeur(s) :** *SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES SCRAS Société par actions simplifiée* — FR.

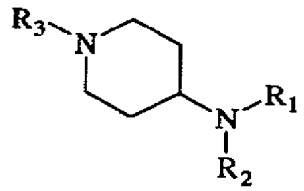
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(73) **Titulaire(s) :**

(74) **Mandataire(s) :** SOCIETE DE CONSEILS ADMINISTRATIFS ET FINANCIERS S.C.A.F.

(54) **DERIVES DE 4-AMINOPIPERIDINE ET LEUR UTILISATION EN TANT QUE MEDICAMENT.**

(57) La présente demande a pour objet de nouveaux dérivés de 4-aminopipéridines de formule



dans laquelle R_1, R_2 et R_3 représentent divers groupes variables, leurs procédés de préparation par des méthodes de synthèse en parallèle en phase liquide et solide. Ces produits ayant une bonne affinité avec certains sous-types de récepteurs de la somatostatine, ils sont particulièrement intéressants pour traiter les états pathologiques ou les maladies dans lesquels un (ou plusieurs) des récepteurs de la somatostatine est (sont) impliqué (s).

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Dérivés de 4-aminopipéridine et leur utilisation en tant que médicament

La présente demande a pour objet de nouveaux dérivés de 4-aminopipéridines et leurs procédés de préparation par des méthodes de synthèse en parallèle en phase liquide et solide. Ces produits ayant une bonne affinité avec certains sous-types de récepteurs de la somatostatine, ils sont particulièrement intéressants pour traiter les états pathologiques ou les maladies dans lesquels un (ou plusieurs) des récepteurs de la somatostatine est (sont) impliqué(s).

La somatostatine (SST) est un tétradécapeptide cyclique qui a été isolé pour la première fois de l'hypothalamus en tant que substance inhibitrice de l'hormone de croissance (Brazeau P. et al., *Science* 1973, **179**, 77-79). Elle intervient également en tant que neurotransmetteur dans le cerveau (Reisine T. et al., *Neuroscience* 1995, 67, 777-790 ; Reisine et al., *Endocrinology* 1995, **16**, 427-442). Le clonage moléculaire a permis de montrer que la bioactivité de la somatostatine dépend directement d'une famille de cinq récepteurs liés à la membrane.

L'hétérogénéité des fonctions biologiques de la somatostatine a conduit à des études pour essayer d'identifier les relations structure-activité des analogues peptidiques sur les récepteurs de la somatostatine, ce qui a amené la découverte de 5 sous-types de récepteurs (Yamada et al., *Proc. Natl. Acad. Sci. U.S.A*, **89**, 251-255, 1992 ; Raynor, K. et al, *Mol. Pharmacol.*, **44**, 385-392, 1993). Les rôles fonctionnels de ces récepteurs sont actuellement activement étudiés. Les affinités avec les différents sous-types de récepteurs de la somatostatine ont été associés au traitement des désordres / maladies suivants. L'activation des sous-types 2 et 5 a été associée à la suppression de l'hormone de croissance (GH) et plus particulièrement à celle des adénomes sécrétant GH (acromégalie) et de ceux sécrétant l'hormone TSH. L'activation du sous-type 2 mais pas du sous-type 5 a été associée au traitement des adénomes sécrétant la prolactine. D'autres indications associées avec l'activation des sous-types de récepteurs de la somatostatine sont la resténose, l'inhibition de la sécrétion d'insuline et/ou de glucagon et en particulier le diabète mellitus, l'hyperlipidémie, l'insensiblité à l'insuline, le Syndrome X, l'angiopathie, la

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rétinopathie proliférative, le phénomène de Dawn et la néphropathie; l'inhibition de la sécrétion d'acide gastrique et en particulier les ulcères peptiques, les fistules entérocutanées et pancréaticocutanées, le syndrome du colon irritable, le syndrome de Dumping, le syndrome des diarrhées aqueuses, les diarrhées reliées au SIDA, les diarrhées induites par la chimiothérapie, la pancréatite aiguë ou chronique et les tumeurs gastrointestinales sécrétrices; le traitement du cancer comme les hépatomes; l'inhibition de l'angiogénèse, le traitement des désordres inflammatoires comme l'arthrite; le rejet chronique des allogreffes; l'angioplastie; la prévention des saignements des vaisseaux greffés et des saignements gastrointestinaux. Les agonistes de la somatostatine peuvent aussi être utilisés pour diminuer le poids d'un patient.

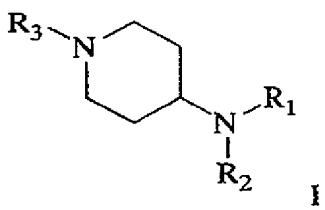
Parmi les désordres pathologiques associés à la somatostatine (Moreau J.P. et al., *Life Sciences*, 1987, **40**, 419 ; Harris A.G. et al., *The European Journal of Medicine*, **1993**, 2, 97-105), on peut donc citer par exemple : l'acromégalie, les adénomes hypophysaires, la maladie de Cushing, les gonadotrophinomes et les prolactinomes, les effets secondaires cataboliques des glucocorticoïdes, le diabète insulinodépendant, la rétinopathie diabétique, la néphropathie diabétique, l'hyperthyroïdie, le gigantisme, les tumeurs gastroentéropancréatiques endocriniennes dont le syndrome carcinoïde, le VIPome, l'insulinome, la nésidioblastose, l'hyperinsulinémie, le glucagonome, le gastrinome et le syndrome de Zollinger-Ellison, le GRFome ainsi que le saignement aigu des varices œsophagiennes, le reflux gastroœsophagien, le reflux gastroduodénal, la pancréatite, les fistules entérocutanées et pancréatiques mais aussi les diarrhées, les diarrhées réfractaires du syndrome d'immunodépression acquise, la diarrhée chronique sécrétoire, la diarrhée associée avec le syndrome de l'intestin irrité, les troubles liés au peptide libérateur de gastrine, les pathologies secondaires aux greffes intestinales, l'hypertension portale ainsi que les hémorragies des varices chez des malades avec cirrhose, l'hémorragie gastro-intestinale, l'hémorragie de l'ulcère gastroduodénale, la maladie de Crohn, les scléroses systémiques, le dumping syndrome, le syndrome du petit intestin, l'hypotension, la sclérodermie et le carcinome thyroïdien médullaire, les maladies liées à l'hyperprolifération cellulaire comme les cancers et plus particulièrement le cancer du sein, le cancer de la prostate, le cancer thyroïdien ainsi

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que le cancer pancréatique et le cancer colorectal, les fibroses et plus particulièrement la fibrose du rein, la fibrose du foie, la fibrose du poumon, la fibrose de la peau, également la fibrose du système nerveux central ainsi que celle du nez et la fibrose induite par la chimiothérapie, et d'autres domaines thérapeutiques comme, par exemple, les céphalées y compris les céphalées associées aux tumeurs hypophysaires, les douleurs, les accès de panique, la chimiothérapie, la cicatrisation des plaies, l'insuffisance rénale résultant d'un retard de croissance, l'obésité et retard de croissance lié à l'obésité, le retard de croissance utérin, la dysplasie du squelette, le syndrome de Noonan, le syndrome d'apnée du sommeil, la maladie de Graves, la maladie polykystique des ovaires, les pseudokystes pancréatiques et ascites, la leucémie, le méningiome, la cachexie cancéreuse, l'inhibition des H pylori, le psoriasis ainsi que la maladie d'Alzheimer. On peut également citer l'ostéoporose.

Les déposants ont trouvé que les composés de formule générale décrits ci-après présentaient une affinité et une sélectivité pour les récepteurs de la somatostatine. Comme la somatostatine et ses analogues peptidiques ont souvent une mauvaise biodisponibilité par voie orale et une faible sélectivité (Robinson, C., *Drugs of the Future*, 1994, **19**, 992; Reubi, J.C. et al., *TIPS*, 1995, **16**, 110), lesdits composés, agonistes ou antagonistes non-peptidiques de la somatostatine, peuvent être avantageusement utilisés pour traiter les états pathologiques ou les maladies tels que présentés ci-dessus et dans lesquels un (ou plusieurs) des récepteurs de la somatostatine est (sont) impliqué(s). De manière préférentielle, lesdits composés peuvent être utilisés pour le traitement de l'acromégalie, des adénomes hypophysaires ou des tumeurs gastroentéropancréatiques endocriniennes dont le syndrome carcinoïde.

La présente invention a donc pour objet des composés de formule générale



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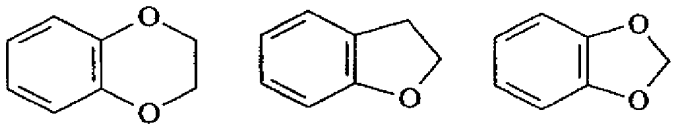
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sous forme racémique, d'énantiomère ou toutes combinaisons de ces formes, dans laquelle :

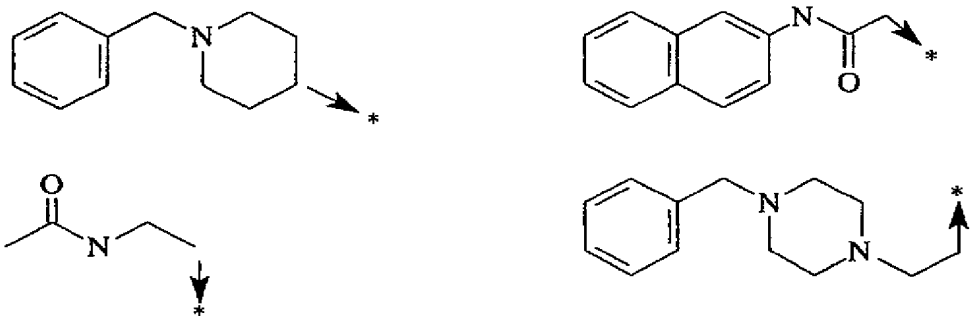
R_1 représente un radical $(C_1\text{-}C_{16})$alkyle linéaire ou ramifié, alkényle, alkynyle, $-(CH_2)_m\text{-}Y\text{-}Z_{11}$ ou $-(CH_2)_m\text{-}Z_{12}$ dans lequel

Z_{11} représente un $(C_1\text{-}C_6)$alkyle ou aryle éventuellement substitué,

Z_{12} représente cyano, cyclohexényle, *bis*-phényle, $(C_3\text{-}C_7)$cycloalkyle, $(C_3\text{-}C_7)$hétérocycloalkyle éventuellement substitué, aryle éventuellement substitué ou hétéroaryle éventuellement substitué,
ou bien Z_{12} représente un radical de formule



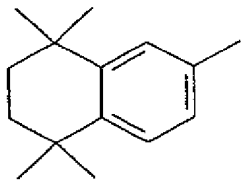
ou bien R_1 représente un radical de formule

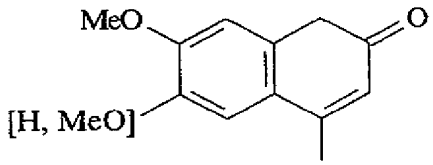


R_2 représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 ;

R_3 représente l'atome d'hydrogène, un radical alkyle éventuellement substitué, alkényle, alkynyle, aralkyle éventuellement susbtitué, hétéroarylalkyle éventuellement substitué, ou un radical de formule $-C(Y)\text{-}NHX_1$, $-(CH_2)_n\text{-}C(O)X_2$, SO_2X_3 ou

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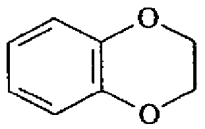


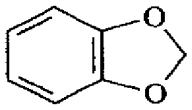


X_1 représente un radical $(C_1\text{-}C_{15})$alkyle linéaire ou ramifié, alkényle, alkynyle, $-(CH_2)_m\text{-}Y\text{-}Z_{21}$ ou $-(CH_2)_pZ_{22}$ dans lequel

Z_{21} représente un $(C_1\text{-}C_6)$alkyle

Z_{22} représente cyclohexényle, indanyle, *bis*-phényle, $(C_3\text{-}C_7)$cycloalkyle, $(C_3\text{-}C_7)$hétérocycloalkyle, mono- ou di-alkylamino, -C(O)-O-alkyle, ou aryle ou hétéroaryle éventuellement substitué,
ou Z_{22} représente un radical de formule

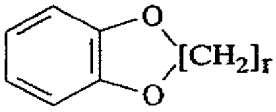




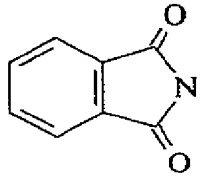
X_2 représente un radical $(C_1\text{-}C_{10})$alkyle linéaire ou ramifié, alkényle éventuellement substitué par un radical phényle (le radical phényle étant lui-même éventuellement substitué), alkynyle, ou un radical de formule $-(CH_2)_m\text{-}W\text{-}(CH_2)_q\text{-}Z_{23}$ ou $-(CH_2)_p\text{-}U\text{-}Z_{24}$ dans lequel

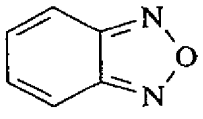
Z_{23} représente un $(C_1\text{-}C_6)$alkyle ou aryle éventuellement substitué ;

Z_{24} représente alkyle, cyclohexényle, *bis*-phényle, $(C_3\text{-}C_7)$cycloalkyle éventuellement substitué, $(C_3\text{-}C_7)$hétérocycloalkyle, cyano, amino, mono ou di-alkylamino, ou aryle ou hétéroaryle éventuellement substitué,
ou Z_{24} représente un radical de formule

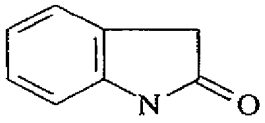
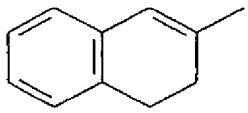


r = 1,2 ou 3

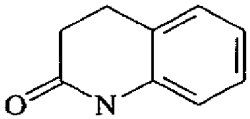
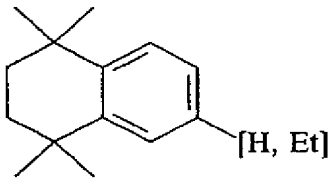


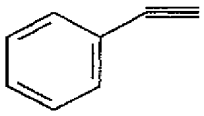
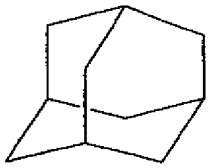
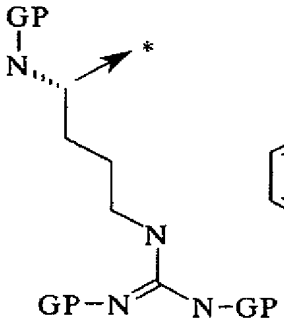


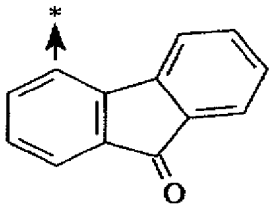
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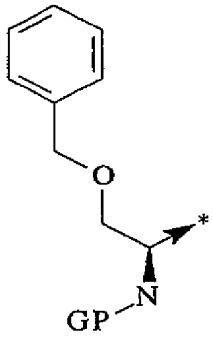



ou bien X_2 représente un radical représenté ci-dessous :

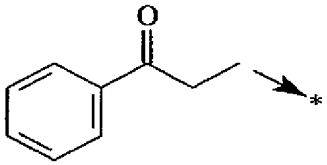



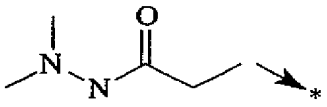




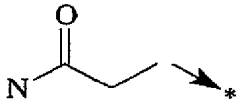


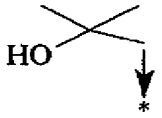


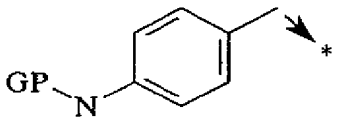
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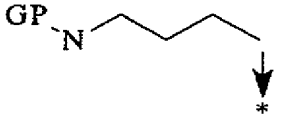


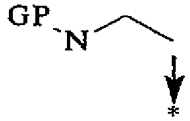


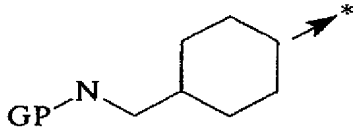










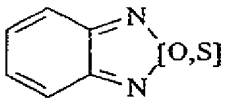


où le groupe protecteur (GP) représente H ou le *tert*-butyloxycarbonyle ;

X_3 représente un radical (C_1-C_{10})alkyle linéaire ou ramifié, alkényle éventuellement substitué par un radical phényle (le radical phényle étant lui-même éventuellement substitué), CF_3, ou $-(CH_2)_pZ_{25}$ dans lequel

Z_{25} représente aryle ou hétéroaryle éventuellement substitué,

ou bien X_3 représente un radical de formule



éventuellement substitué par un ou plusieurs radicaux halo identiques ou différents ;

Y représente un atome d'oxygène ou de soufre ;

W représente un atome d'oxygène, de soufre ou SO_2 ;

U représente une liaison covalente ou l'atome d'oxygène ;

n est un entier de 0 à 4 ;

m est un entier de 1 à 6 ;

p est un entier de 0 à 6 ;

q est un entier de 0 à 2,

ou leurs sels d'addition avec les acides minéraux ou organiques pharmaceutiquement acceptables.

L'invention a plus particulièrement pour objet les produits de formule générale I telle que définie ci-dessus, caractérisée en ce que

i) le ou les substituant(s) que peuvent porter les radicaux aryle que représentent Z_{11} et Z_{12} et hétéroaryle que représente Z_{12} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, $-CF_3$, $-OCF_3$, phényle, phénoxy, aminosulfonyle ;

ii) le ou les substituant(s) que peut porter le radical hétérocycloalkyle que représente Z_{12} sont choisis indépendamment parmi les radicaux oxy et alkyle ;

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iii) le ou les substituant(s) que peut porter les radicaux aryle et hétéroaryle que représente Z_{22} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkényle, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, aminosulfonyle, pipéridinosulfonyle, mono- ou di-alkylamino, -C(O)-O-alkyle, -C(O)-alkyle, ou phényle, phénoxy, phénylthio, benzyloxy, le radical phényle pouvant être substitué ;

iv) le ou les substituant(s) que peut porter les radicaux aryle que représente Z_{23} et Z_{24}, cycloalkyle et hétéroaryle que représente Z_{24} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3, OCF_3, $OCHF_2$, SCF_3, nitro, cyano, azido, hydroxy, -C(O)O-alkyle, -O-C(O)-alkyle, -NH-C(O)-alkyle, alkylsulfonyle, mono- ou di-alkylamino, amino, aminoalkyle, pyrrolyle, pyrrolydinyle ou bien les radicaux phényle, phénoxy, phénylthio, benzyle, benzyloxy dont le radical aryle est éventuellement substitué par un ou plusieurs radicaux alkyle, CF_3 ou halo ;

v) le ou les substituant(s) que peut porter les radicaux aryle et hétéroaryle que représente Z_{25} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3, OCF_3, nitro, cyano, -NH-C(O)-alkyle, alkylsulfonyle, amino, mono- et di-alkylamino, phényle, pyridino ;

vi) le substituant que peut porter le radical alkyle que représente R_3 est le radical cyano.

vii) le ou les substituant(s) que peut porter le radical aralkyle que représente R_3 sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3, OCF_3, $OCHF_2$, SCF_3, $SCHF_2$, nitro, cyano, -C(O)O-alkyle, alkylsulfonyle, thiadiazolyle, ou bien les radicaux phényle et phénoxy dont le radical phényle est éventuellement substitué par un ou plusieurs radicaux halo.

viii) le ou les substituant(s) que peut porter le radical hétéroarylalkyle que représente R_3 sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo ou nitro.

Dans les définitions indiquées ci-dessus, l'expression halo représente le radical fluoro, chloro, bromo ou iodo, de préférence chloro, fluoro ou bromo. L'expression

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alkyle (lorsqu'il n'est pas donné plus de précision), représente de préférence un radical alkyle ayant de 1 à 6 atomes de carbone, linéaire ou ramifié, tels que les radicaux méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, sec-butyle et tert-butyle, pentyle ou amyle, isopentyle, neopentyle, hexyle ou isohexyle. Parmi les radicaux alkyle contenant de 1 à 15 atomes de carbone, on peut citer les alkyles tels que définis ci-dessus mais également les radicaux heptyle, octyle, nonyle, décyle, dodécyle, tridécyle ou pentadécyle.

Par alkényle, lorsqu'il n'est pas donné plus de précision, on entend un radical alkyle linéaire ou ramifié comptant de 1 à 6 atomes de carbone et présentant au moins une insaturation (double liaison), comme par exemple vinyle, allyle, propényle, butènyle ou pentènyle. Par alkynyle, lorsqu'il n'est pas donné plus de précision, on entend un radical alkyle linéaire ou ramifié comptant de 1 à 6 atomes de carbone et présentant au moins une double insaturation (triple liaison) comme par exemple un radical éthynyle, propargyle, butynyle ou pentynyle.

Le terme cycloalkyle désigne un système monocyclique carboné comprenant de 3 à 7 atomes de carbone, et de préférence les cycles cyclopropyle, cyclobutyle, cyclopentyle ou cyclohexyle. L'expression hétérocycloalkyle désigne un cycloalkyle saturé contenant de 2 à 7 atomes de carbones et au moins un hétéroatome. Ce radical peut contenir plusieurs hétéroatomes identiques ou différents. De préférence, les hétéroatomes sont choisis parmi l'oxygène, le soufre ou l'azote. Comme exemples d'hétérocycloalkyle, on peut citer le cycle pyrrolidine, pyrrolidinone, imidazolidine, pyrrazolidine, isothiazolidine, thiazolidine, isoxazolidine, pipéridine, pipérazine ou morpholine.

Les radicaux alkoxy peuvent correspondre aux radicaux alkyle indiqués ci-dessus comme par exemple les radicaux méthoxy, éthoxy, propyloxy ou isopropyloxy mais également butoxy linéaire, secondaire ou tertiaire, pentyloxy. Le terme alkylthio inférieur désigne de préférence les radicaux dans lesquels le radical alkyle est tel que défini ci-dessus comme par exemple méthylthio, éthylthio. Le terme alkylsulfonyle désigne de préférence les radicaux dans lesquels le radical alkyle est tel que défini ci-dessus.

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L'expression aryle représente un radical aromatique, constitué d'un cycle ou de cycles condensés, comme par exemple le radical phényle ou naphtyle. L'expression hétéroaryle désigne un radical aromatique, constitué d'un cycle ou de cycles condensés, avec au moins un cycle contenant un ou plusieurs hétéroatomes identiques ou différents choisis parmi le soufre, l'azote ou l'oxygène. Comme exemple de radical hétéroaryle, on peut citer les radicaux thiényle, furyle, pyrrolyle, imidazolyle, pyrazolyle, isothiazolyle, thiazolyle, isoxazolyle, oxazolyle, triazolyle, pyridyle, pyrazinyle, pyrimidyle, quinolyle, isoquinolyle, quinoxalinyle, benzothiényle, benzofuryle, indolyle, benzoxadiazoyle.

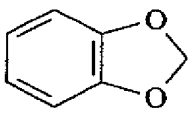
Les termes mono- et di-alkylamino désignent de préférence les radicaux dans lesquels les radicaux alkyle sont tels que définis ci-dessus, comme par exemple méthylamino, éthylamino, diméthylamino, diéthylamino ou (méthyl)(éthyl)amino.

La présente invention a plus particulièrement pour objet des composés de formule générale I telle que définie ci-dessus dans laquelle :

R_1 représente un radical $(C_1\text{-}C_6)$alkyle linéaire ou ramifié, le radical $-(CH_2)_m\text{-}Y\text{-}Z_{11}$ ou $-(CH_2)_m\text{-}Z_{12}$ dans lequel

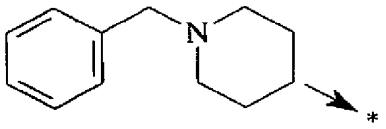
Z_{11} représente un $(C_1\text{-}C_6)$alkyle,

Z_{12} représente *bis*-phényle, $(C_3\text{-}C_7)$cycloalkyle, $(C_3\text{-}C_7)$hétérocycloalkyle éventuellement substitué, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy,
ou bien Z_{12} représente



Y représente l'atome d'oxygène,

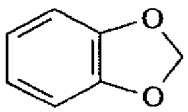
ou bien un radical de formule



R_2 représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical $(C_1\text{-}C_{15})$alkyle linéaire ou ramifié, ou $-(CH_2)_pZ_{22}$ dans lequel

Z_{22} représente cyclohexényle, *bis*-phényle, $(C_3\text{-}C_7)$cycloalkyle, $(C_3\text{-}C_7)$hétérocycloalkyle, mono- ou di-alkylamino, -C(O)-O-alkyle, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, pipéridinosulfonyle, –C(O)-O-alkyle, -C(O)-alkyle, ou phényle,
ou bien Z_{22} représente un radical de formule



X_2 représente un radical $(C_1\text{-}C_{10})$alkyle linéaire ou ramifié, alkynyle, $-(CH_2)_m\text{-}W\text{-}(CH_2)_q\text{-}Z_{23}$ ou $-(CH_2)_p\text{-}U\text{-}Z_{24}$ dans lequel

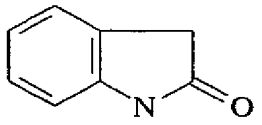
W représente SO_2,

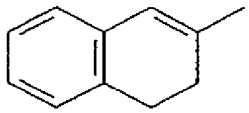
U représente une liaison covalente,

Z_{23} représente un radical aryle ;

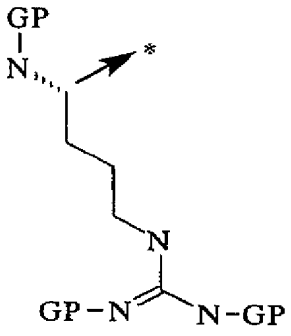
Z_{24} représente cyclohexényle, *bis*-phényle, $(C_3\text{-}C_7)$cycloalkyle éventuellement substitué par un radical aminoalkyle, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo, alkyle, alkoxy, $-CF_3$, $-OCF_3$, SCF_3, hydroxy, -O-C(O)-alkyle, mono- ou di-alkylamino, amino
ou Z_{24} représente un radical de formule

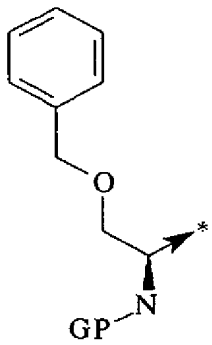
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ou bien X_2 représente





X_3 représente un radical $-(CH_2)_pZ_{25}$ dans lequel Z_{25} représente un radical aryle éventuellement substitué par un ou plusieurs radicaux identiques ou différents choisis parmi alkoxy et CF_3,

R_3 représente l'atome d'hydrogène, un radical alkyle, alkényle, hétéroarylalkyle éventuellement substitué ou un radical de formule $-C(Y)-NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical $-(CH_2)_pZ_{22}$ dans lequel

Z_{22} représente un radical aryle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3, nitro, phénoxy ;

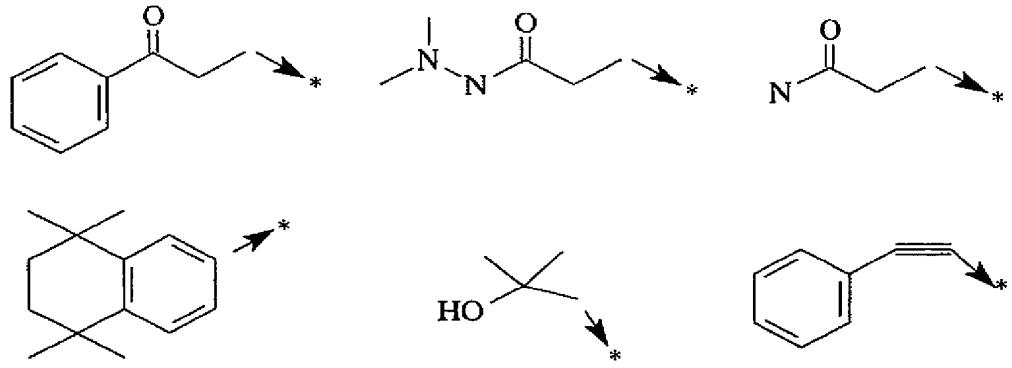
X_2 représente le radical vinyle substitué par un phényle, le radical phényle étant lui-même éventuellement substitué par un ou plusieurs radicaux halo, ou $-(CH_2)_p$-U-Z_{24} dans lequel

Z_{24} représente alkyle, $(C_3$-$C_7)$cycloalkyle, $(C_3$-$C_7)$hétérocycloalkyle, *bis*-phényle, amino, mono ou di-alkylamino, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis parmi

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alkoxy, bromo, chloro, fluoro, hydroxy, CF_3, nitro, amino, mono- et di-alkylamino, pyrrolyle,

ou bien X_2 représente un radical de formule



X_3 représente un radical $(C_1\text{-}C_{10})$alkyle linéaire ou ramifié, le radical vinyle substitué par un radical (le radical phényle étant lui-même éventuellement substitué), CF_3, ou $-(CH_2)_pZ_{25}$ dans lequel

Z_{25} représente aryle ou hétéroaryle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3, nitro, -NH-C(O)-alkyle, mono- et di-alkylamino.

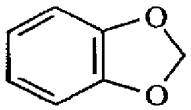
De manière préférentielle, R_1 représente un radical $(C_1\text{-}C_6)$alkyle linéaire ou ramifié, le radical $-(CH_2)_m\text{-}Y\text{-}Z_{11}$ ou $-(CH_2)_m\text{-}Z_{12}$ dans lequel

Z_{11} représente un $(C_1\text{-}C_6)$alkyle,

Z_{12} représente naphtyle, morpholino, *bis*-phényle, pyrrolidinyle substitué par le radical oxy, ou bien les radicaux phényle, pipérazinyle, pyridinyle et indolyle qui sont éventuellement substitués par un ou plusieurs substituants choisis indépendamment parmi les radicaux bromo, fluoro, chloro, alkyle, alkoxy, $-CF_3$, $-OCF_3$;

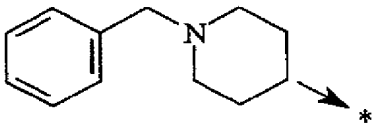
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ou bien Z_{12} représente



Y représente l'atome d'oxygène,

ou bien R_1 représente un radical de formule ci-dessous:

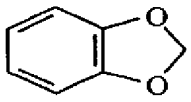


De manière préférentielle, R_2 représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical $(C_1\text{-}C_{10})$alkyle linéaire ou ramifié, ou $-(CH_2)_pZ_{22}$ dans lequel

Z_{22} représente cyclohexyle, cyclohexényle, *bis*-phényle, morpholino, pipéridino, mono- ou di-alkylamino, -C(O)-O-alkyle, ou phényle, naphtyle ou furyle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, pipéridinosulfonyle, –C(O)-O-alkyle, -C(O)-alkyle ou phényle,

ou bien Z_{22} représente un radical de formule



X_2 représente un radical alkyle, alkynyle, $-(CH_2)_m\text{-}W\text{-}(CH_2)_q\text{-}Z_{23}$ ou $-(CH_2)_pZ_{24}$ dans lequel

W représente SO_2 ;

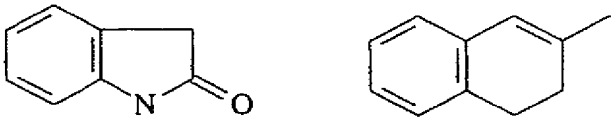
Z_{23} représente le radical phényle ;

Z_{24} représente cyclohexényle, *bis*-phényle, cyclohexyle éventuellement substitué par un radical aminoalkyle, ou phényle, naphtyle, benzothiényle, thiényle ou indolyle éventuellement substitué par un ou

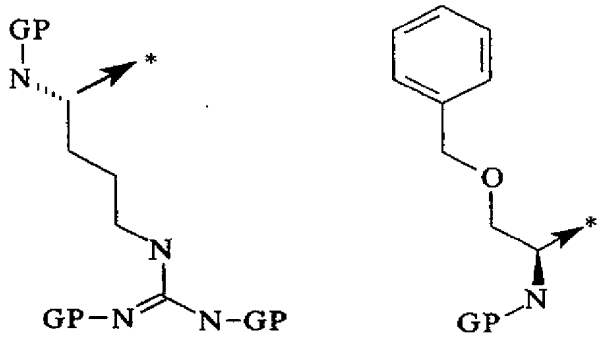
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plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo, alkyle, alkoxy, -CF_3, -OCF_3, SCF_3, hydroxy, -O-C(O)-alkyle, -NH-C(O)-alkyle, mono- ou di-alkylamino, amino, ou

Z_{24} représente un radical de formule



ou bien X_2 représente



X_3 représente un radical $-(CH_2)_pZ_{25}$ dans lequel Z_{25} représente le radical phényle éventuellement substitué par un ou plusieurs radicaux identiques ou différents choisis parmie alkoxy et CF_3 ,

De manière préférentielle, R_3 représente l'atome d'hydrogène, un radical alkyle, alkényle ou furyl-méthyl susbtitué par un ou plusieurs radicaux nitro, ou un radical de formule $-C(Y)-NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical $-(CH_2)_pZ_{22}$ dans lequel

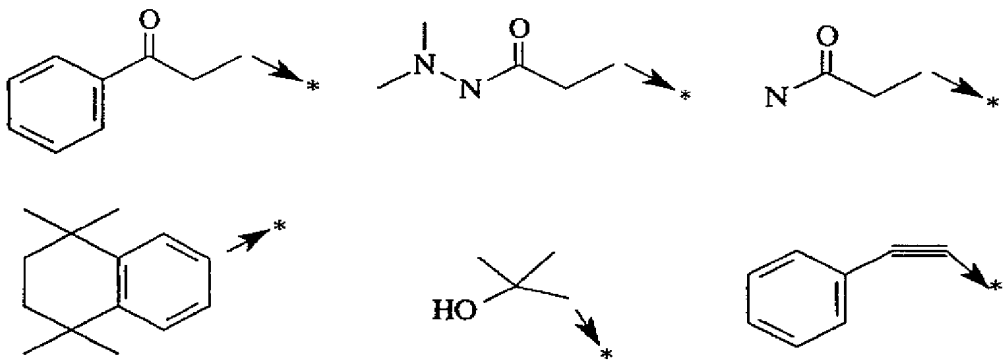
Z_{22} représente le radical phényle ou naphtyle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3, nitro, phénoxy,

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X_2 représente le radical vinyle substitué par un radical phényle lui-même éventuellement substitué par un ou plusieurs radicaux halo, ou $-(CH_2)_p$-U-Z_{24} dans lequel

Z_{24} représente alkyle, cyclohexyle, tétrahydrofuryle, *bis*-phényle, amino, mono ou di-alkylamino, ou phényle, indolyle, thiényle, pyridinyle, benzothiényle et furyle éventuellement substitué par un ou plusieurs radicaux choisis parmi alkoxy, bromo, chloro, fluoro, amino, mono- et di-alkylamino, nitro, hydroxy, pyrrolyle

ou bien X_2 représente un radical de formule



X_3 représente un radical (C_1-C_{10})alkyle linéaire ou ramifié, le radical vinyle substitué par un radical phényle, CF_3, ou $-(CH_2)_pZ_{25}$ dans lequel

Z_{25} représente un radical phényle, napthyle, thiényle, pyrazolyle ou thiazolyle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3, nitro, -NH-C(O)-alkyle, mono- et di-alkylamino ;

De manière très préférentielle, R_1 représente le radical $-(CH_2)_mZ_{12}$ dans lequel m = 2 et Z_{12} représente *bis*-phényle ou bien le radical indolyle substitués par un ou plusieurs substituants choisis indépendamment parmi les radicaux alkyle et alkoxy.

De manière très préférentielle, R_2 représente les radicaux de formule $-C(Y)NHX_1$ et $-C(O)X_2$ dans laquelle

Y représente S ;

X_1 représente un radical phényle éventuellement substitué par un ou plusieurs radicaux azido,

X_2 représente $-(CH_2)_pZ_{24}$ dans lequel

p est égal à 1, 2 ou 3,

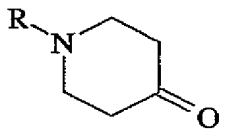
Z_{24} représente cyclohexyle, ou phényle ou benzothiényle éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo ou $-CF_3$.

De manière très préférentielle, R_3 représente l'atome d'hydrogène ou le radical méthyle.

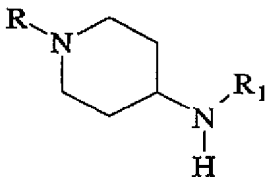
Les composés selon l'invention peuvent être préparés en phase solide ou liquide.

L'invention a également pour objet un procédé de préparation, en phase liquide, de composés de formule I selon l'invention, caractérisé en ce qu'il comprend

l'amination réductrice de la pipéridone N-substituée suivante



dans laquelle R représente le radical méthyle ou Boc, en présence d'une amine de formule R_1NH_2 dans laquelle R_1 a la signification indiquée ci-dessus, pour obtenir le composé de formule 1

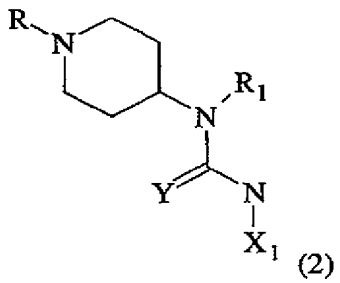


(1)

composé de formule (1) que l'on fait réagir avec

A) soit un composé de formule $X_1NC(Y)$ dans laquelle X_1 et Y ont la signification indiquée ci-dessus, pour obtenir un composé de formule (2)

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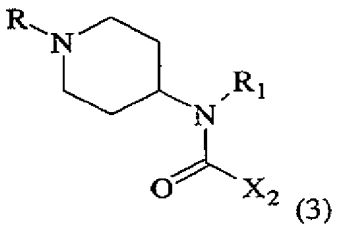


(2)

composé de formule (2) qui représente le composé de formule (I) correspondant dans lequel R_3 représente Me ou Boc et qui, lorsque R_3 représente Boc, peut être soumis à un traitement acide pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

composé de formule (I) ainsi obtenu que l'on peut faire réagir avec un composé de formule $X_1NC(Y)$, X_2CO_2H ou bien X_3SO_2Cl dans laquelle X_1, Y, X_2 et X_3 ont la signification indiquée ci-dessus, pour obtenir le composé de formule I correspondant dans laquelle R_2 représente un radical de formule $-C(Y)NHX_1$ et R_3 le radical $-C(Y)-NHX_1$, $-C(O)X_2$ ou SO_2X_3 respectivement ;

B) soit un composé de formule X_2CO_2H dans laquelle X_2 a la signification indiquée ci-dessus, pour obtenir un composé de formule (3)



(3)

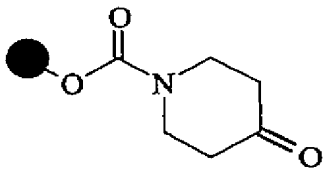
composé de formule (3) qui représente le composé de formule (I) correspondant dans lequel R_3 représente Me ou Boc et qui, lorsque R_3 représente Boc, peut être soumis à un traitement acide pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

composé de formule (I) ainsi obtenu que l'on peut faire réagir avec un composé de formule $X_1NC(Y)$, X_2CO_2H ou bien X_3SO_2Cl dans laquelle X_1, Y, X_2 et X_3 ont la signification indiquée ci-dessus, pour obtenir le composé de formule I correspondant dans laquelle R_2 représente un radical de formule $-C(O)X_2$ et R_3 le radical $-C(Y)-NHX_1$, $-C(O)X_2$ ou SO_2X_3 respectivement.

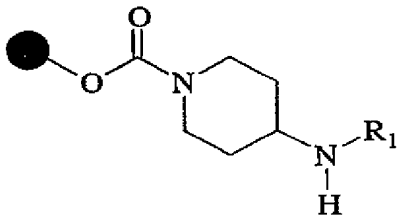
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L'invention a également pour objet un procédé de préparation, en phase solide, de composés de formule I selon l'invention, caractérisé en ce qu'il comprend

l'amination réductrice de la résine cétonique



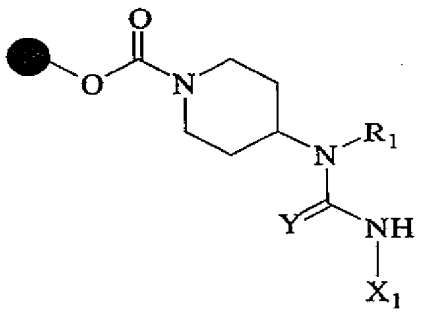
en présence d'une amine de formule R_1NH_2 dans laquelle R_1 a la signification indiquée ci-dessus, pour obtenir le composé de formule (4)



(4)

composé de formule (4) que l'on fait réagir avec

A) soit un composé de formule $X_1NC(Y)$ dans laquelle X_1 et Y ont la signification indiquée ci-dessus, pour obtenir un composé de formule (5)

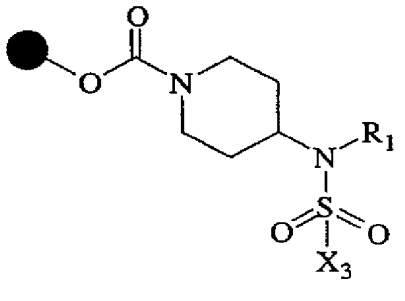


(5)

suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

B) soit un composé de formule X_3SO_2Cl dans laquelle X_3 a la signification indiquée ci-dessus, pour obtenir un composé de formule (6)

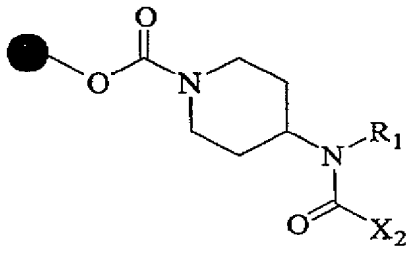
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(6)

suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

C) soit un composé de formule X_2CO_2Cl dans laquelle X_2 a la signification indiquée ci-dessus, pour obtenir un composé de formule (7)



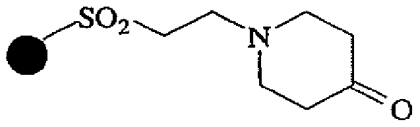
(7)

suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène ;

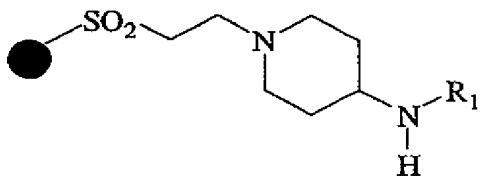
D) soit un composé de formule X_2CO_2H dans laquelle X_2 a la signification indiquée ci-dessus, pour obtenir un composé de formule (7) tel que défini ci-dessus, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène.

L'invention a également pour objet un procédé de préparation, en phase solide, de composés de formule I selon l'invention, caractérisé en ce qu'il comprend

l'amination réductrice de la résine cétonique



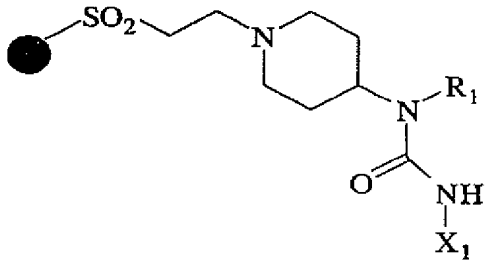
en présence d'une amine de formule R_1NH_2 dans laquelle R_1 a la signification indiquée ci-dessus, pour obtenir le composé de formule (8)



(8)

composé de formule (8) que l'on fait réagir avec

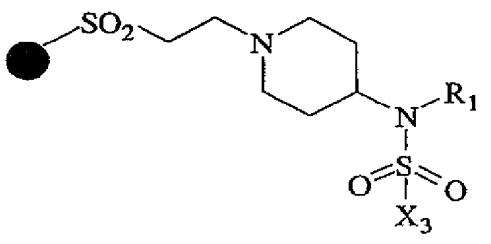
A) soit un composé de formule $X_1NC(O)$ dans laquelle X_1 a la signification indiquée ci-dessus, pour obtenir un composé de formule (9)



(9)

composé (9) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini ci-dessus et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant ;

B) soit un composé de formule X_3SO_2Cl dans laquelle X_3 a la signification indiquée ci-dessus, pour obtenir un composé de formule (10)

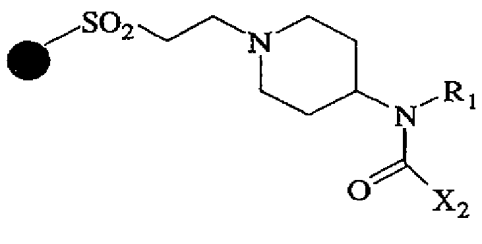


(10)

composé (10) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini ci-dessus et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant ;

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C) soit un composé de formule X_2CO_2Cl dans laquelle X_2 a la signification indiquée ci-dessus, pour obtenir un composé de formule (11)



(11)

composé (11) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini ci-dessus et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant ;

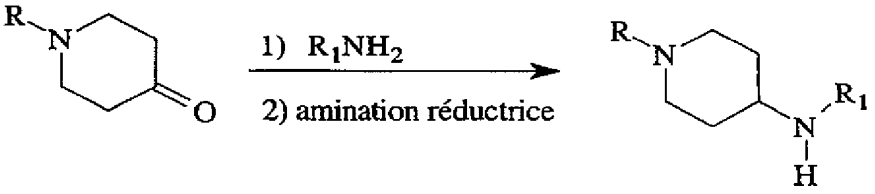
D) soit un composé de formule X_2CO_2H dans laquelle X_2 a la signification indiquée ci-dessus, pour obtenir un composé de formule (11) tel que défini ci-dessus,

composé (11) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini ci-dessus et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant.

A) Synthèses en phase liquide *via* la pipéridone N-substituée

A1) Amination réductrice

Elle s'effectue selon l'étape suivante :

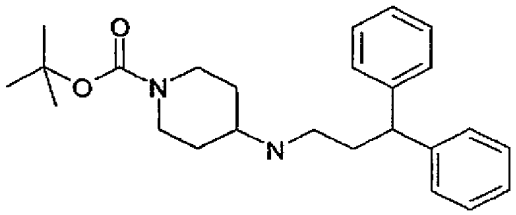


dans laquelle R représente méthyle ou Boc et R_1 a la signification indiquée ci-dessus.

La procédure générale est la suivante : l'amination réductrice (Abdel-Magid, A.F. ; Maryanoff, C.A. ; Carson, K.G. *Tetrahedron Lett.* **1990**, *31*, 5595-5598 ; Abdel-Magid, A.F. ; Carson, K.G. ; Harris, B.D. ; Maryanoff, C.A. ; Shah, R.D., *J. Org. Chem.* **1996**, *61*, 3849-3862) de la pipéridone N-substituée est réalisée dans des solvants anhydres chlorés tel que le dichloroéthane en présence d'une amine primaire (1,1 à 1,5 éq.), d'un agent réducteur tel que le triacétoxyborohydrure de sodium (1,1

à 1,5 éq.) et d'acide acétique (10 % en masse relatif à la pipéridone N-substituée). Le mélange réactionnel est agité pendant 1 à 4 heures à température ambiante. Dans certains cas, une solution de soude (0.1 M) est ajoutée et le mélange agité pendant 20 à 90 minutes. Sinon, le mélange réactionnel est lavé avec une solution saturée de bicarbonate de sodium, chlorure de sodium, séché sur sulfate de magnésium, filtré et concentré. Le produit désiré est purifié par chromatographie flash sur gel de silice.

Préparation 1 : Carboxylate de tert-butyl 4-[(3,3-diphénylpropyl)amino]-1-pipéridine ($C_{25}H_{34}N_2O_2$, M = 394,56)

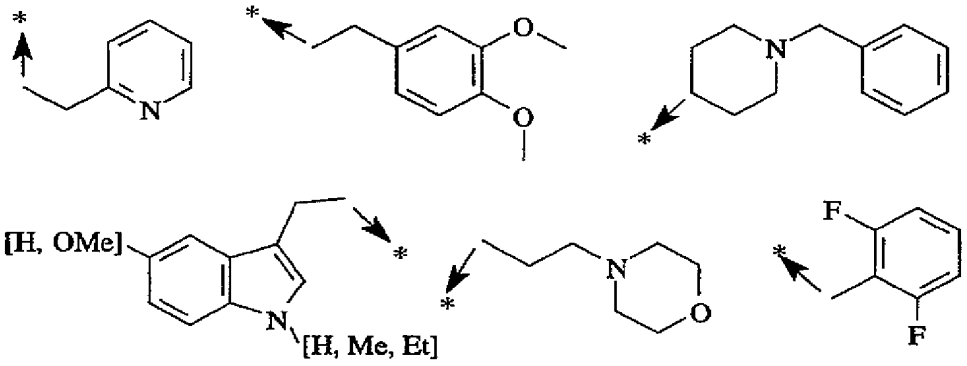


A 5 g (25 mmol) de N-Boc-pipéridone dans 100 ml de dichloroéthane sec est ajouté la 3,3-diphénylpropylamine (5,8 g, 27,5 mmol), le triacétoxyborohydrure de sodium (6,36 g, 30 mmol) et 0,5 ml d'acide acétique. La solution jaune trouble est agitée à température ambiante pendant 1 heure. 50 ml d'une solution de soude (0.1 M) sont alors ajoutés et le mélange agité pendant 30 minutes. La phase organique est lavée avec une solution saturée de bicarbonate de sodium, de chlorure de sodium, séchée sur sulfate de magnésium, filtrée et concentrée pour donner 10 g d'un solide jaune. Ce solide est purifié par chromatographie flash sur gel de silice en éluant avec un mélange heptane/acétate d'éthyle (4/1, 3 /1, 2/1 puis 1/1) puis à l'acétate d'éthyle pur. Les fractions sont concentrées sous vide pour donner 5,6 g (rdt = 57 %) d'un solide jaune pale.

RMN ^{1}H (CD_3OD, 400 MHz) δ : 7,27 (m, 8H) ; 7,16 (m, 2H) ; 4 (dd, J = 6,4 et 14Hz, 3H) ; 2,73 (m, 2H) ; 2,55 (m, 3H) ; 2,26 (q, J = 7,6Hz, 2H) ; 1,78 (d, J = 12Hz, 2H) ; 1,45 (s, 9H) ; 1,15 (qd, J = 4,4 et 12,8Hz, 2H). SM/CL : m/z = 395,2 (M+H).

Une série de 4-aminosubstitué-1-pipéridine est préparée selon cette procédure avec les autres groupes R_1 suivants :

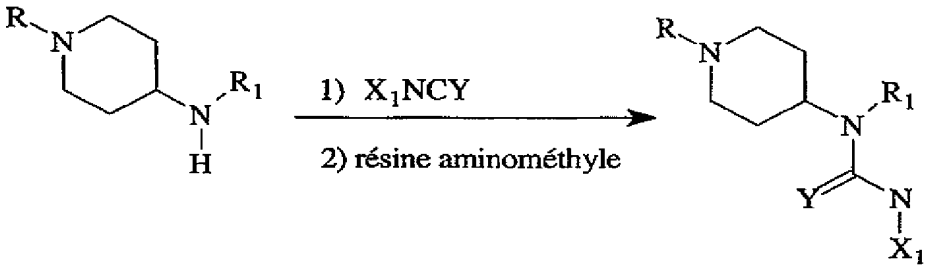
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A2) Fonctionalisation des pipéridines

A2a) Synthèses d'urées et de thiourées

Les synthèses d'urées et de thiourées sont mises en œuvre selon la procédure décrite dans la littérature (Kaldor, S.W. ; Siegel, M.G. ; Fritz, J.E. ; Dressman, B.A. ; Hahn, P.J. *Tetrahedron Lett.* **1996**, *37*, 7193-7196 ; Kaldor, S.W. ; Fritz, J.E. ; Tang, J. ; McKinney, E.R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3041-3044 ; Booth, R.J. ; Hodges, J.C. *J. Am. Chem. Soc.* **1997**, *119*, 4882-4886 ; Flynn, D.L. ; Crich, J.Z. ; Devraj, R.V. ; Hockerman, S.L. ; Parlow, J.J. ; South, M.S. ; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874-4881) suivant le schéma suivant :



dans laquelle R représente méthyle ou Boc et X_1 et Y ont la signification indiquée ci-dessus. Il est à noter que dans le cas où R représente Boc, le produit ainsi obtenu est un produit final répondant à la formule I selon l'invention mais peut également être utilisé comme intermédiaire de synthèse.

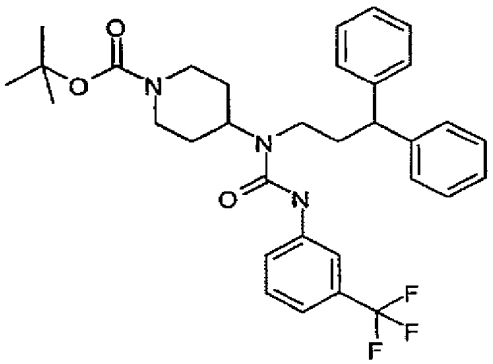
La procédure générale est la suivante : l'isocyanate ou l'isothiocyanate (1,1 à 1,5 éq.) est ajouté à la 4-aminosubstitué-1-pipéridine dans des solvants aprotiques tels que le dichlorométhane, le tétrahydrofurane ou la diméthylformamide et le mélange est agité de 45 minutes à 18 heures à température ambiante. La résine aminométhyle (Novabiochem, 1,33 mmol/g, 0,2 à 1 éq.) est ajoutée et le mélange agité de

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45 minutes à 18 heures. Dans certains cas, de la résine basique échangeuse d'ions telle que la IRA-68 (Gayo, L.M. ; Suto, M.J. *Tetrahedron Lett.* **1997**, *38*, 513-516) peut être ajoutée. Les résines sont filtrées et le filtrat concentré. D'autres purifications sur cartouche de gel de silice ou d'alumine basique (500 mg, Interchim) peuvent éventuellement être réalisées.

Exemple A2a : Carboxylate de tert-butyl-4-((3,3-diphénylpropyl) {[3-(trifluoro méthyl) anilino] carbonyl}amino)-1-pipéridine

($C_{33}H_{38}F_3N_3O_3$, M = 581,68)

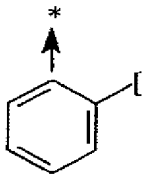


A une solution de carboxylate de *tert*-butyl 4-[(3,3-diphénylpropyl)amino]-1-pipéridine (470 mg, 1,2 mmol) dans 5 ml de dichlorométhane est ajouté 246 mg (1,32 mmol) d'isocyanate de 3-(trifluorométhyl)phényle. La solution est agitée 45 minutes, et la résine aminométhyle (180 mg, 0,36 mmol) est ajoutée et la réaction remise sur l'agitateur orbital pendant 45 minutes. La résine est filtrée et lavée au dichlorométhane. Le filtrat est concentré *in vacuo* pour donner 610 mg (rdt = 87 %) d'une mousse blanche.

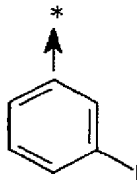
RMN ^1H (CD_3OD, 400 MHz) δ : 7,71 (s, 1H) ; 7,57 (d, 1H) ; 7,43 (t, 1H) ; 7,26 (m, 10H) ; 7,15 (m, 1H) ; 4,1 (m, 3H) ; 3,97 (dd, J = 7,6 et 10Hz, 1H) ; 3,17 (m, 2H) ; 2,75 (m, 2H) ; 2,35 (m, 2H) ; 1,65 (d, J = 12Hz, 2H) ; 1,46 (s, 9H, groupe *t*butyle) ; 1,39 (dd, J = 2,4 et 10,8Hz, 2H) ; 1,29 (s, 1H). SM/CL : m/z = 582 (M+H).

Pour les groupes R_1 tels qu'illustrés au point A1 ci-dessus, les groupes X_1 que l'on peut envisager pour la synthèse d'urées (Y = O) selon la procédure ci-dessus, sont les suivants :

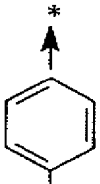
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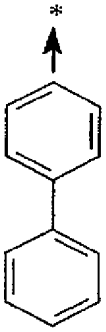
[H, Br, F, Cl, OMe, SMe, OEt, CF_3, Me, Et, nPr, iPr, tBu, Ph, NO_2, CN]

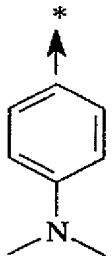


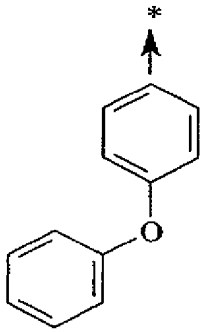
[OMe, COMe, CF_3, Br, F, Cl, Me, Et, NO_2, CN, SMe]

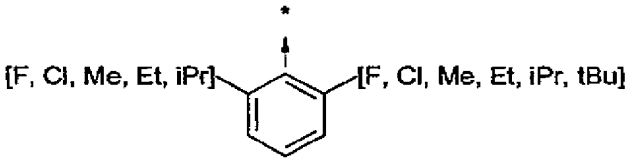


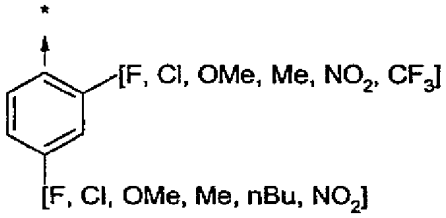
[SMe, CO_2Et, OCF_3, OnBu, Br, F, Cl, OMe, CF_3, Me, NO_2, OEt, Et, iPr, nBu, CN]

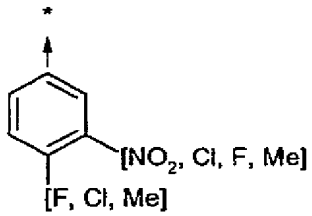


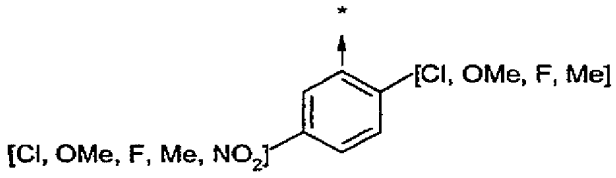


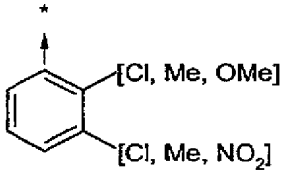


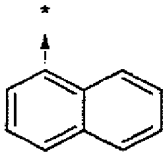

[F, Cl, Me, Et, iPr]
[F, Cl, Me, Et, iPr, tBu]

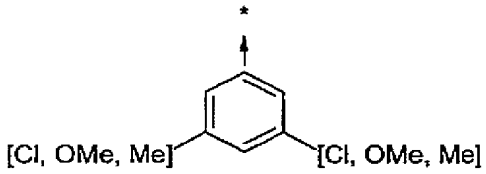

[F, Cl, OMe, Me, NO2, CF3]
[F, Cl, OMe, Me, nBu, NO2]

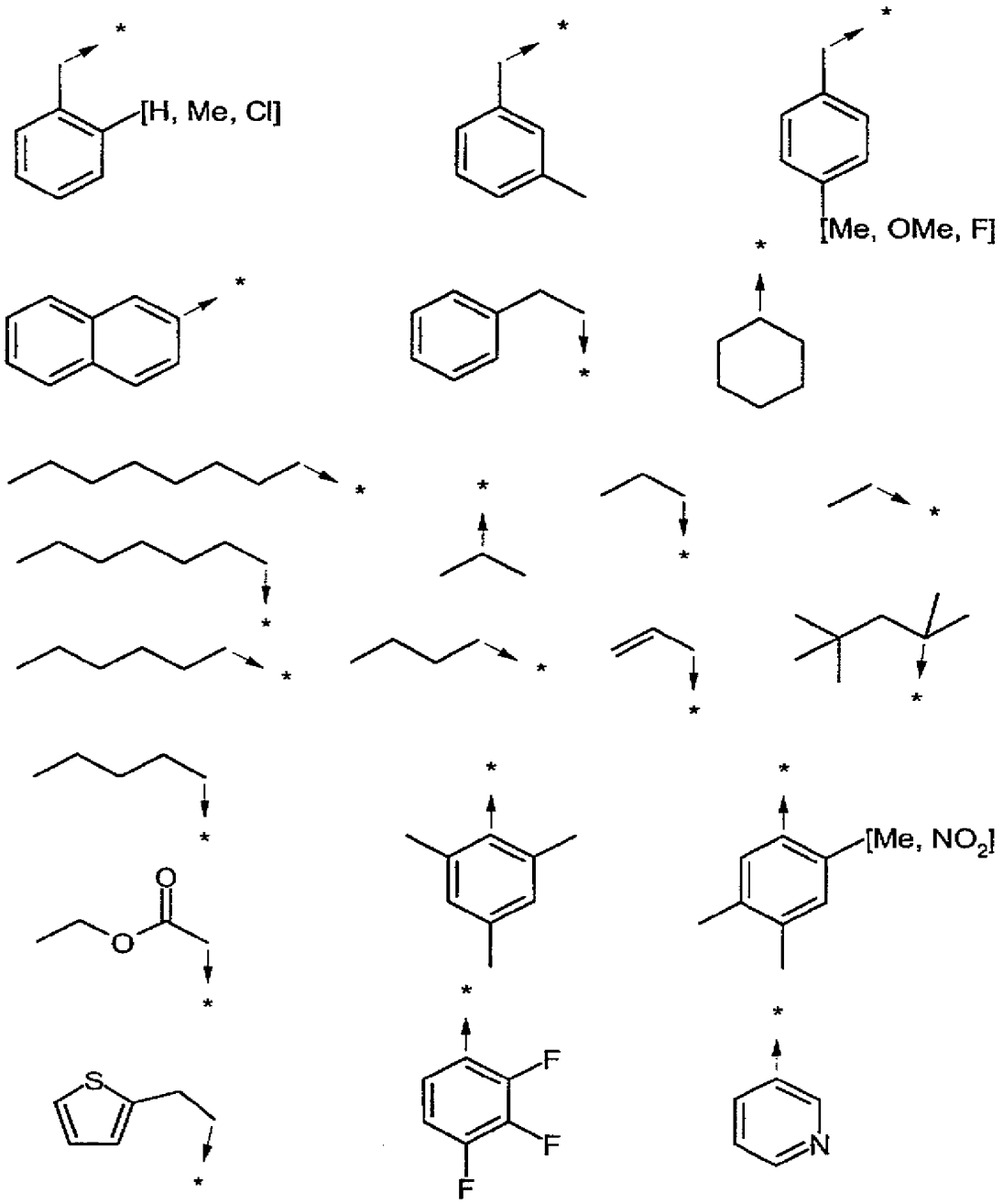

[NO2, Cl, F, Me]
[F, Cl, Me]


[Cl, OMe, F, Me]
[Cl, OMe, F, Me, NO2]

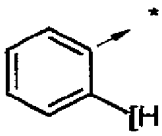

[Cl, Me, OMe]
[Cl, Me, NO2]



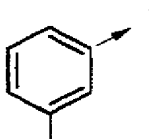

[Cl, OMe, Me]
[Cl, OMe, Me]


[H, Me, Cl]
[Me, OMe, F]
O
O
S
F
F
F
N
[Me, NO2]

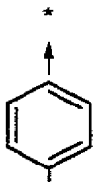
Pour les groupes R_1 tels qu'illustrés au point A1 ci-dessus, les groupes X_1 que l'on peut envisager pour la synthèse de thiourées (Y = S) selon la procédure ci-dessus, sont les suivants :



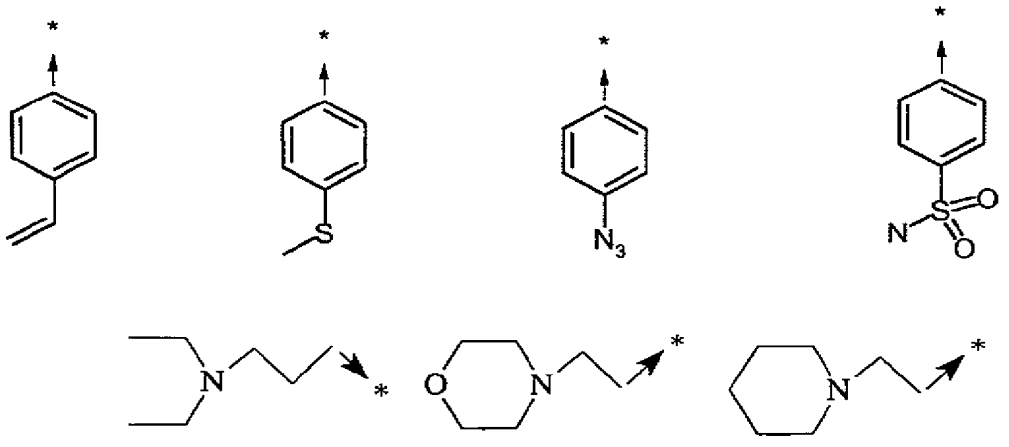
[H, Cl, Br, F, I, OMe, SMe, OEt, CF_3, OCF_3, NO_2, CN, Me, Et, iPr, Ph]



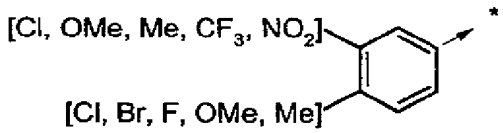
[Cl, Br, F, I, OMe, SMe, CF_3, OCF_3, NO_2, CN, Me, Et, iPr, OCH_2Ph]

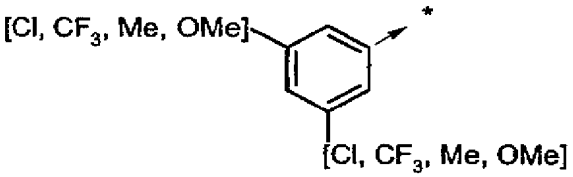


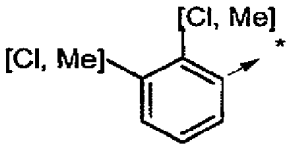
[Cl, Br, F, I, OMe, OEt, CF_3, OCF_3, NO_2, CN, Me, Et, iPr, nBu, tBu, NMe_2, NEt_2]

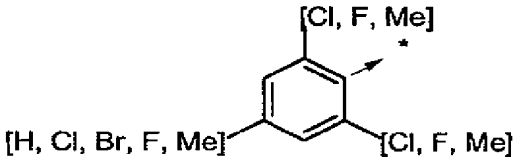


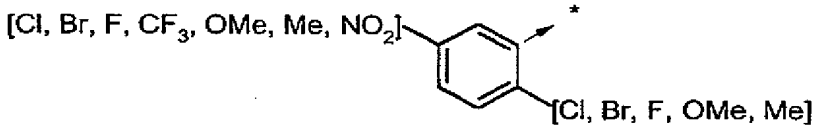
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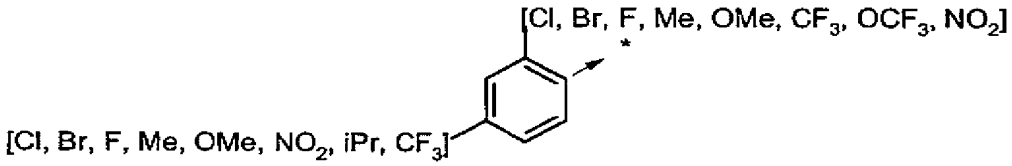

[Cl, OMe, Me, CF_3, NO_2]
[Cl, Br, F, OMe, Me]
*

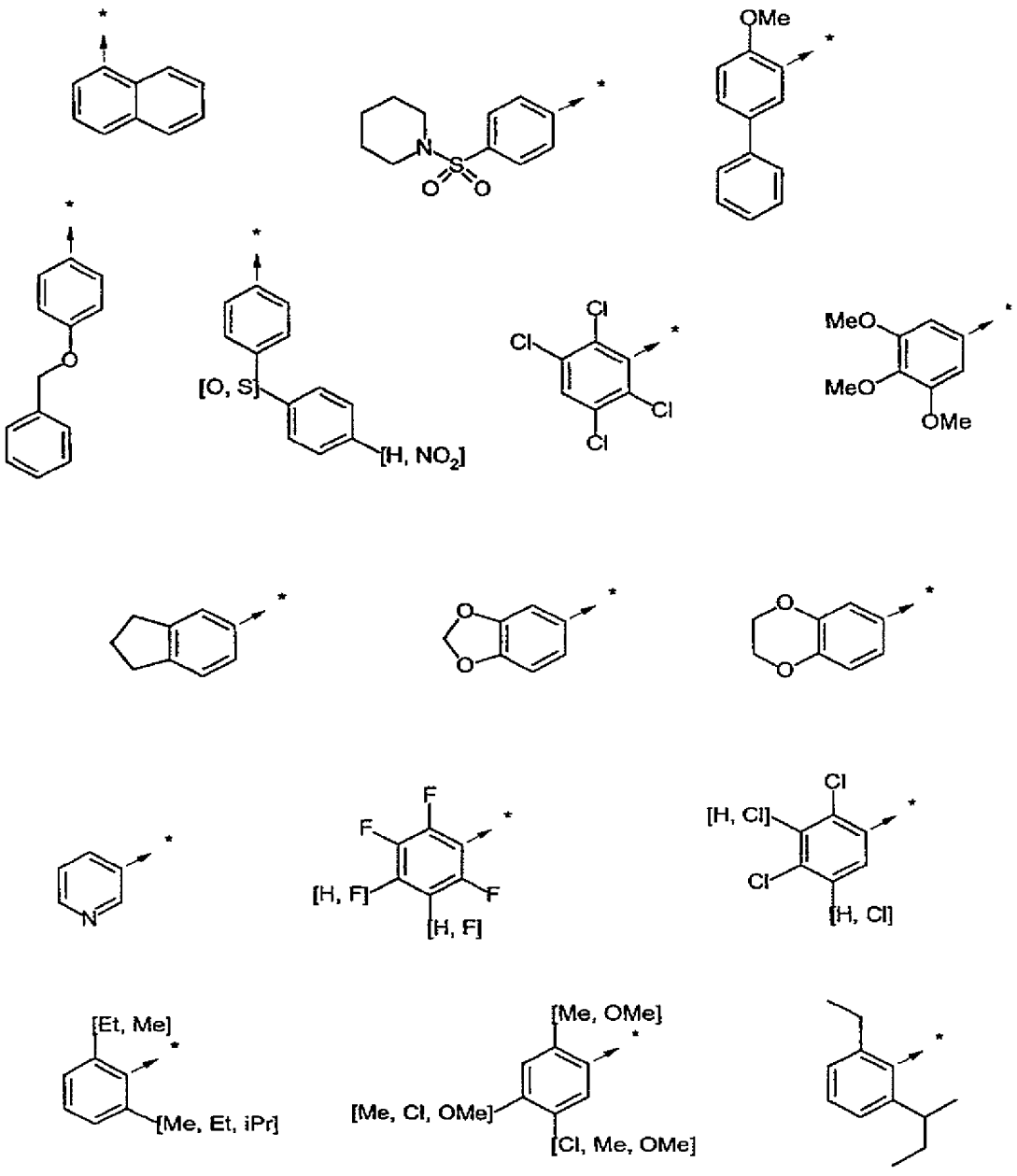

[Cl, CF_3, Me, OMe]
[Cl, CF_3, Me, OMe]
*


[Cl, Me]
[Cl, Me]
*

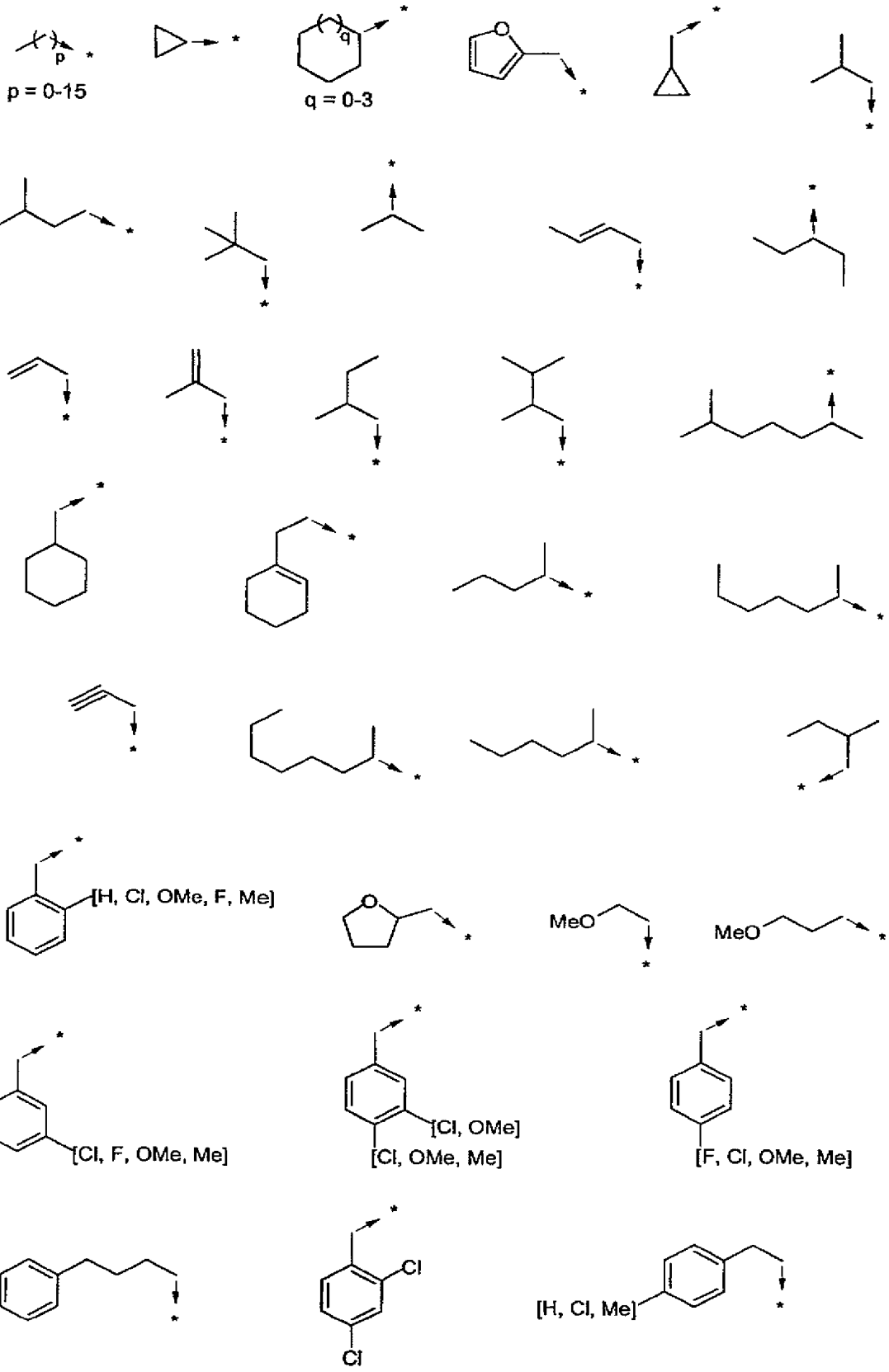

[Cl, F, Me]
*
[H, Cl, Br, F, Me]
[Cl, F, Me]

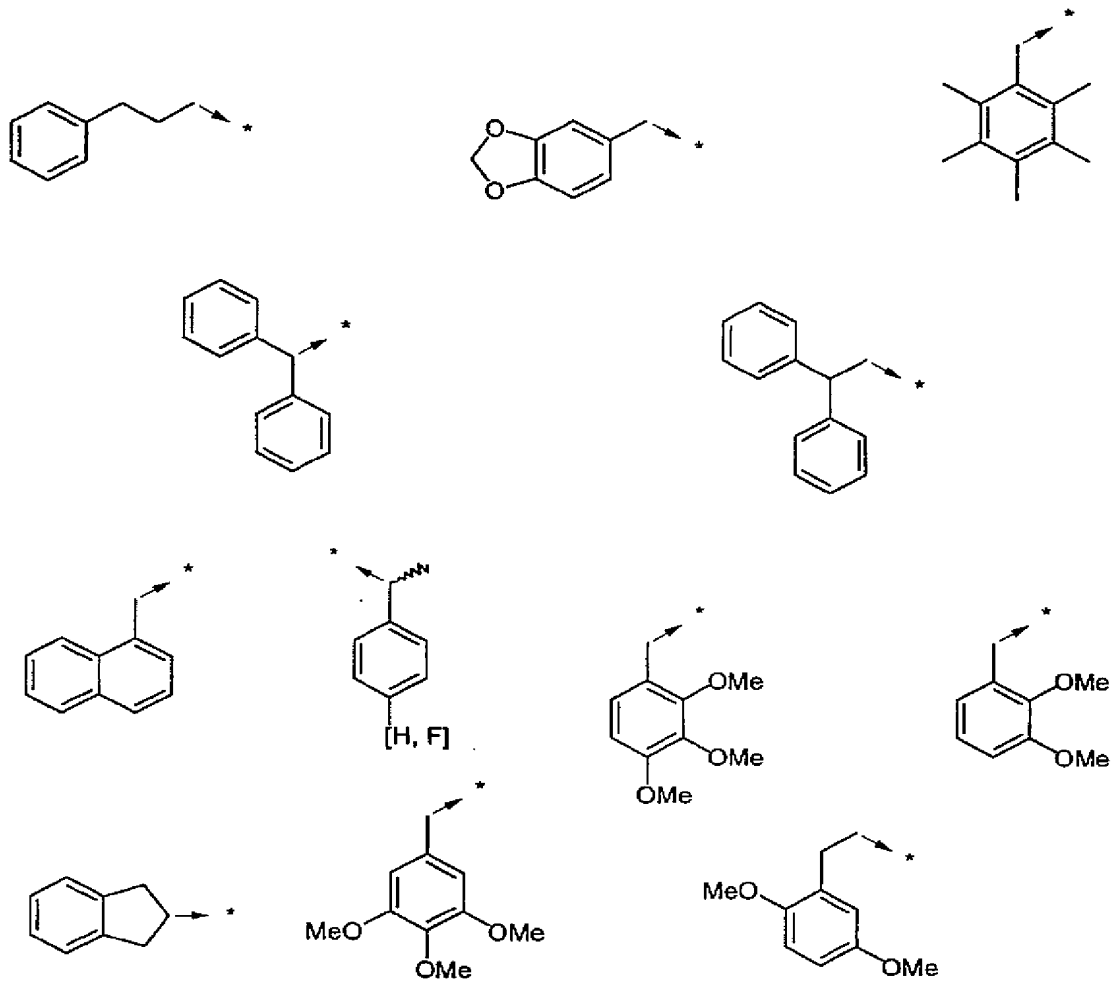

[Cl, Br, F, CF_3, OMe, Me, NO_2]
*
[Cl, Br, F, OMe, Me]


[Cl, Br, F, Me, OMe, CF_3, OCF_3, NO_2]
*
[Cl, Br, F, Me, OMe, NO_2, iPr, CF_3]



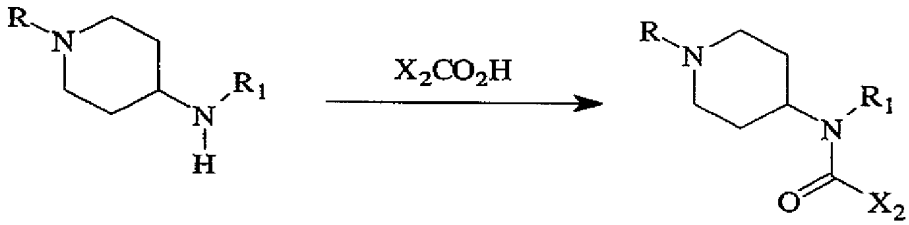
NSDOCID: <FR___2802206A1_I_>


p = 0-15
q = 0-3
[H, Cl, OMe, F, Me]
MeO
MeO
[Cl, F, OMe, Me]
[Cl, OMe]
[Cl, OMe, Me]
[F, Cl, OMe, Me]
Cl
Cl
[H, Cl, Me]



A2b) Synthèse d'amides à partir d'acides carboxyliques

Les synthèses d'amides à partir d'acides carboxyliques sont mises en œuvre selon le schéma réactionnel suivant :

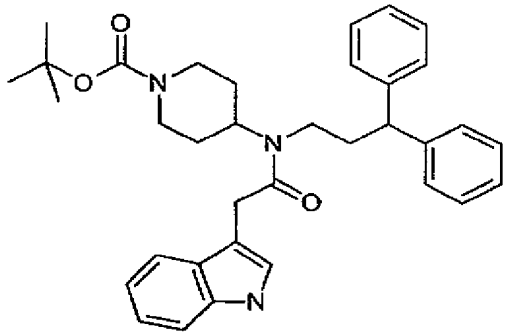


dans laquelle R représente méthyle ou Boc et X_2 a la signification indiquée ci-dessus. Il est à noter que dans le cas où R représente Boc, le produit ainsi obtenu est un produit final répondant à la formule I selon l'invention mais peut également être utilisé comme intermédiaire de synthèse.

\SDOCID: <FR___2802206A1_I_>

La procédure générale est la suivante : l'acide carboxylique (1,1 à 2,5 éq.) dissout dans un solvant aprotique anhydre tel que le dichlorométhane, la diméthylformamide ou le tétrahydrofurane est activé avec du 1-éthyl-3-(3-diméthylaminopropyl) carbodiimide greffé sur résine (P-EDC, Novabiochem, 2,33 mmol/g, 1,3 à 3 éq.) (Desai, M.C. ; Stephens Stramiello, L.M. *Tetrahedron Lett.* **1993**, *34*, 7685-7688). Ce mélange est agité 5 à 30 minutes à température ambiante. La 4-aminosubstitué-1-pipéridine prédissoute dans un solvant aprotique anhydre tel que le dichlorométhane, la diméthylformamide ou le tétrahydrofurane est alors ajouté et le mélange réactionnel agité à température ambiante 1 à 18 heures. Dans certains cas, de la résine basique échangeuse d'ions (IRA-68, SAX) est ajoutée et le mélange à nouveau agité à température ambiante 1 à 18 heures. Les résines sont filtrées sur fritté ou sur cartouche de résine basique échangeuse d'ions (IRA-68, SAX) ou sur cartouche d'alumine basique (500 mg, Interchim).

Exemple A2b : Carboxylate de tert-butyl 4-{(3,4-diméthoxyphénéthyl)[2-(1H-indol-3-yl)acétyl]amino}-1-pipéridine ($C_{35}H_{41}N_3O_3$, M = 551,74)

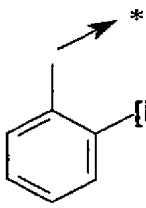


512 mg (1,12 mmol, 1,4 éq.) de résine P-EDC est prégonflée dans le dichlorométhane. L'acide 2-(1*H*-indol-3-yl)acétique (153 mg, 0,875 mmol, 1,1 éq.) est ajouté et le mélange agité 10 minutes. Le carboxylate de *tert*-butyl 4-[(3,3-diphénylpropyl)amino]-1-pipéridine (292 mg, 0,8 mmol) dans le tétrahydrofurane est ajouté et la réaction agitée toute la nuit. 2 spatules de résine basique échangeuse d'ions IRA-68 sont ajoutées et la réaction agitée à nouveau toute la nuit. Les résines sont filtrées et le filtrat est concentré sous vide pour donner 250 mg (rdt = 86 %) d'une mousse jaune pâle.

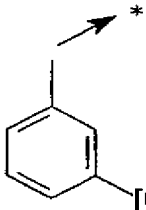
SDOCID: <FR___2802206A1_I_>

RMN ^1H (CD_3OD, 400 MHz) δ : 7,63 (d, J = 8Hz, 1H) ; 7,44 (d, J = 8Hz, 1H) ; 7,36 (d, J = 8Hz, 1H) ; 7,26 (d, J = 8Hz, 1H) ; 7,2 (m, 6H) ; 7,13 (m, 3H) ; 7,1 (m, 2H) ; 6,68 (s, 1H); 4-3,75 (m, 4H) ; 3,65 (s, 1H) ; 3,2 (m, 1H) ; 3 (m, 1H) ; 2,75 (m, 1H) ; 2,26 (m, 3H) ; 1,6 (m, 2H) ; 1,44 (s, 9H) ; 1,13 (m, 2H). SM/CL : m/z = 552,4 (M+H).

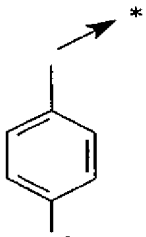
Une série d'amides a été synthétisée selon cette procédure. Les radicaux X_2 que l'on peut envisager sont les suivants :



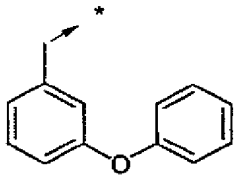
[H, Cl, Br, F, I, OMe, OEt, NO_2, CF_3, OH, Me, OCF_3, SCF_3, $OCHF_2$]

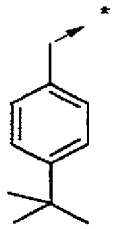


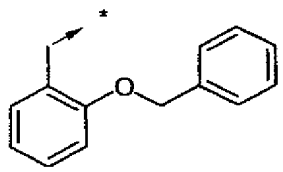
[Cl, Br, F, I, OMe, OEt, NO_2, Me, OH, CF_3, OCF_3, SCF_3, $OCHF_2$]

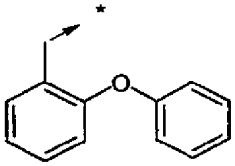


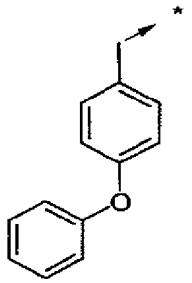
[Cl, Br, F, I, OMe, OEt, OnBu, NO_2, CF_3, Me, OH, NMe_2, Ph, iPr, OCF_3, SCF_3]

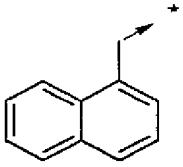


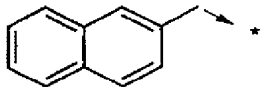


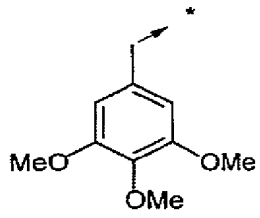


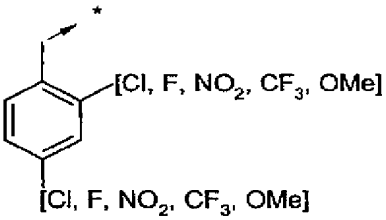


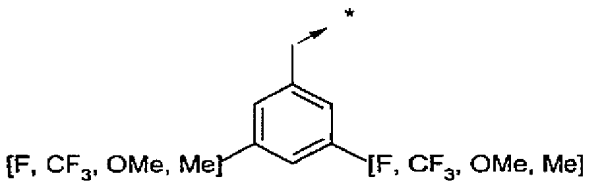


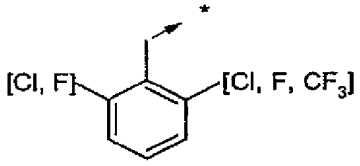


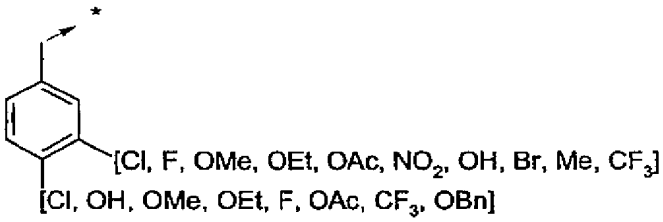


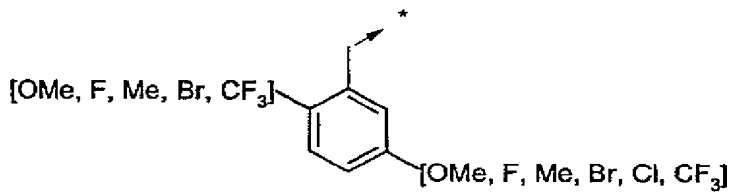

MeO
OMe
OMe

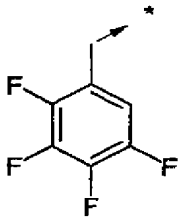

[Cl, F, NO2, CF3, OMe]
[Cl, F, NO2, CF3, OMe]

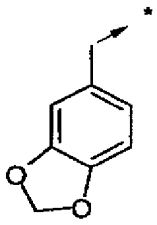

[F, CF3, OMe, Me]
[F, CF3, OMe, Me]

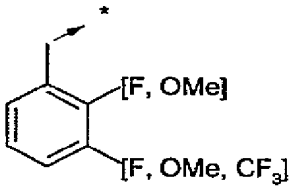

[Cl, F]
[Cl, F, CF3]

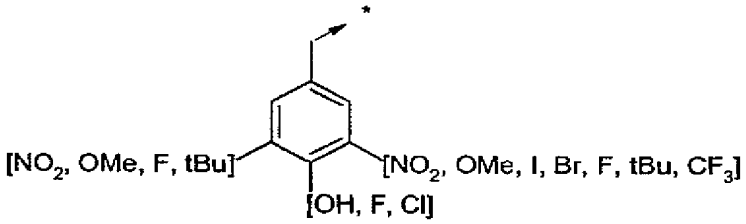

[Cl, F, OMe, OEt, OAc, NO2, OH, Br, Me, CF3]
[Cl, OH, OMe, OEt, F, OAc, CF3, OBn]



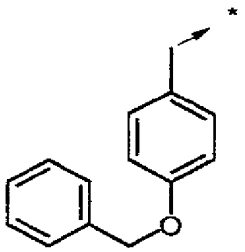


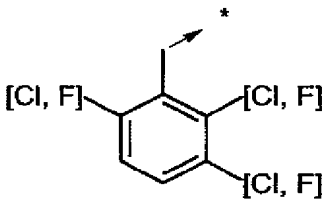


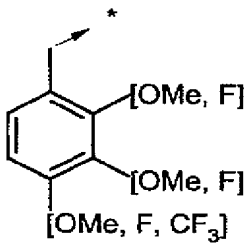


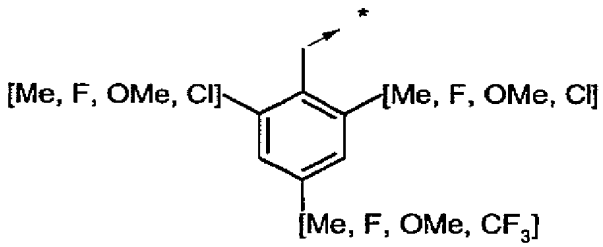


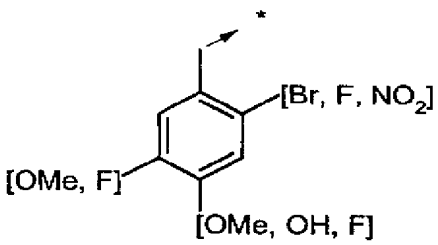
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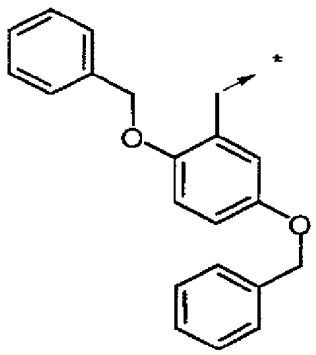


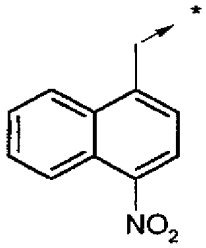

[Cl, F]
[Cl, F]
[Cl, F]


[OMe, F]
[OMe, F]
[OMe, F, CF3]

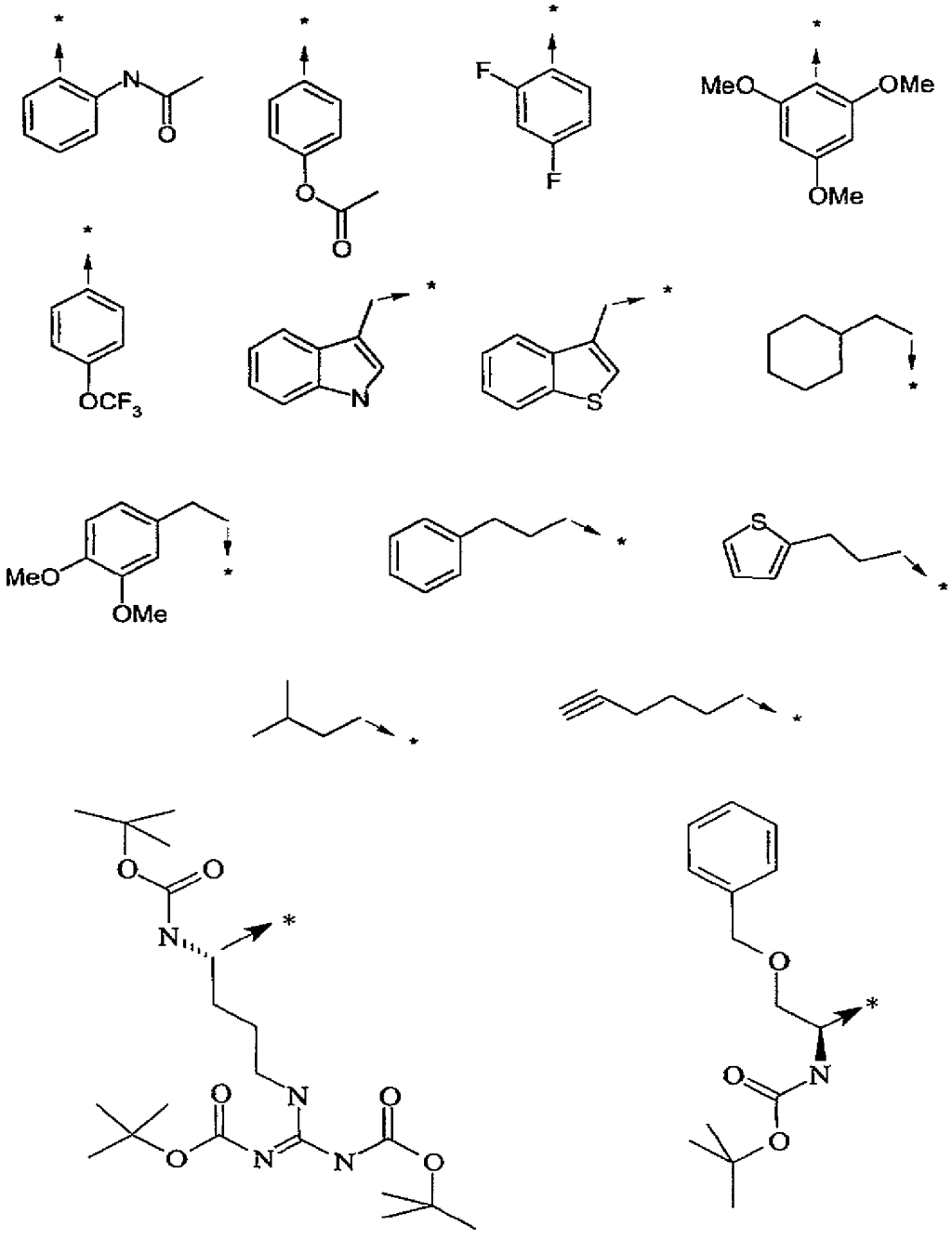

[Me, F, OMe, Cl]
[Me, F, OMe, Cl]
[Me, F, OMe, CF3]


[Br, F, NO2]
[OMe, F]
[OMe, OH, F]

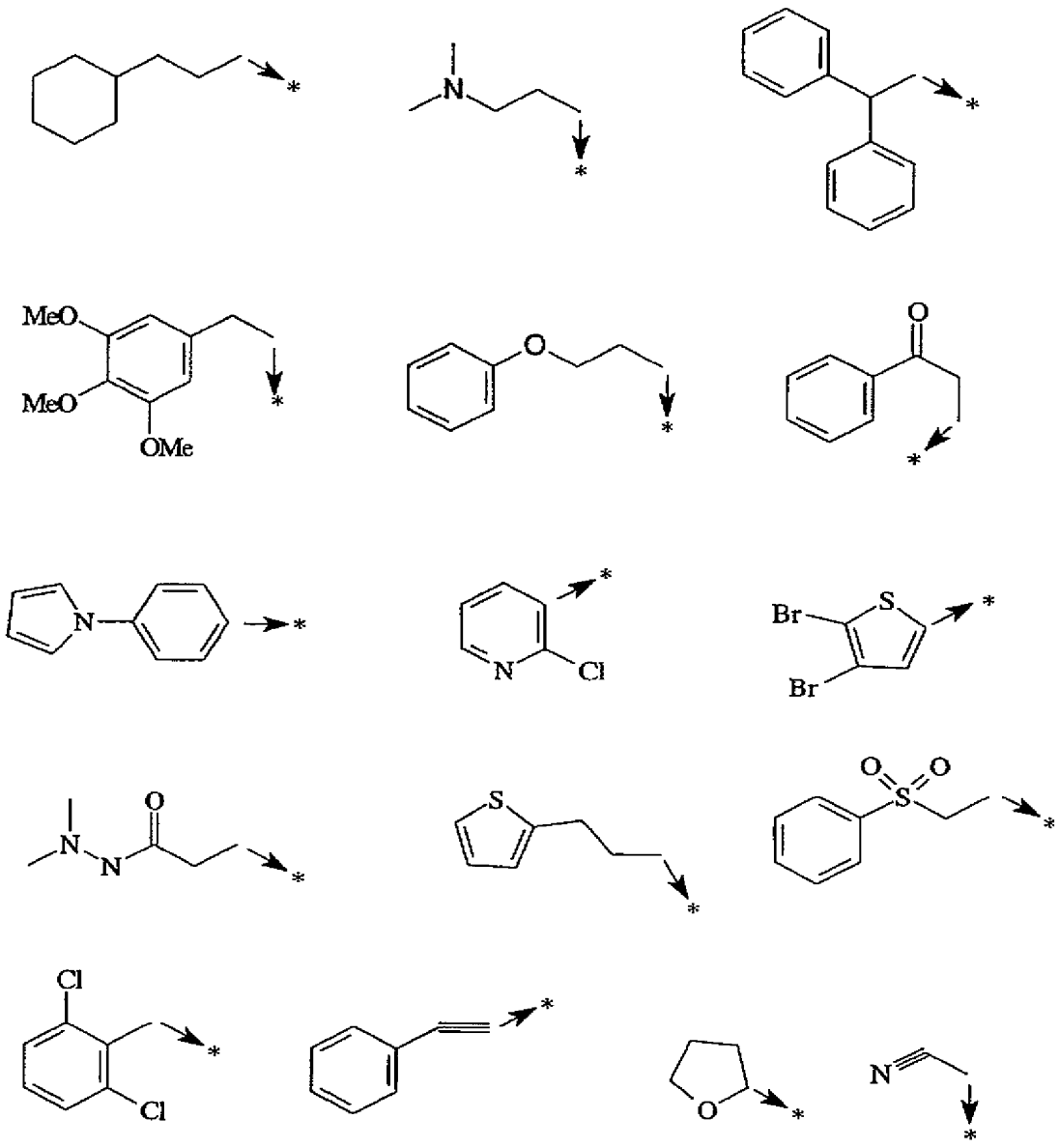


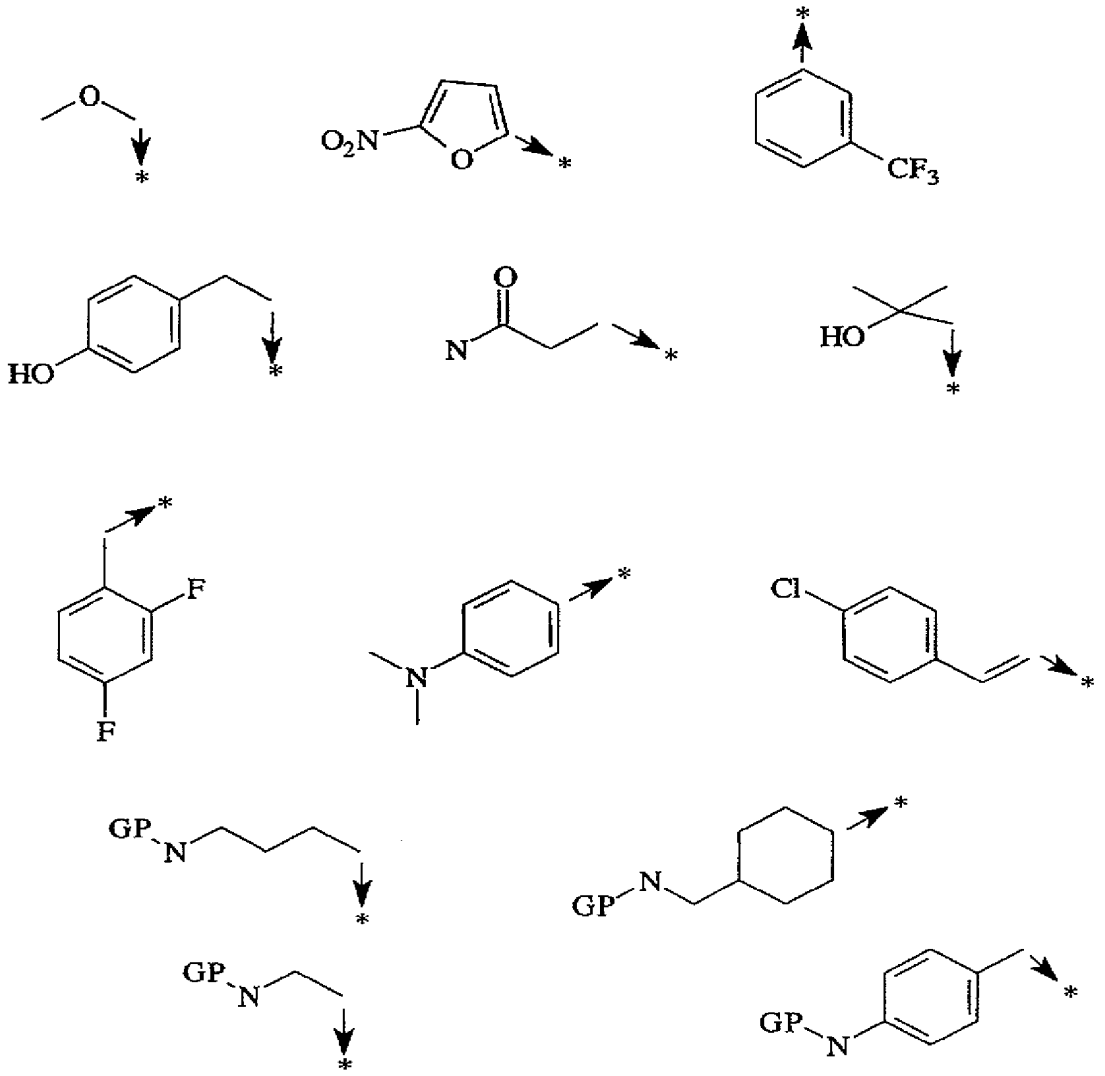

NO2


[SMe, OCHF2, SO2Me]



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MeO
MeO
OMe
N
O
Br
S
Br
Cl
N
O
O
S
O
Cl
Cl
O
N

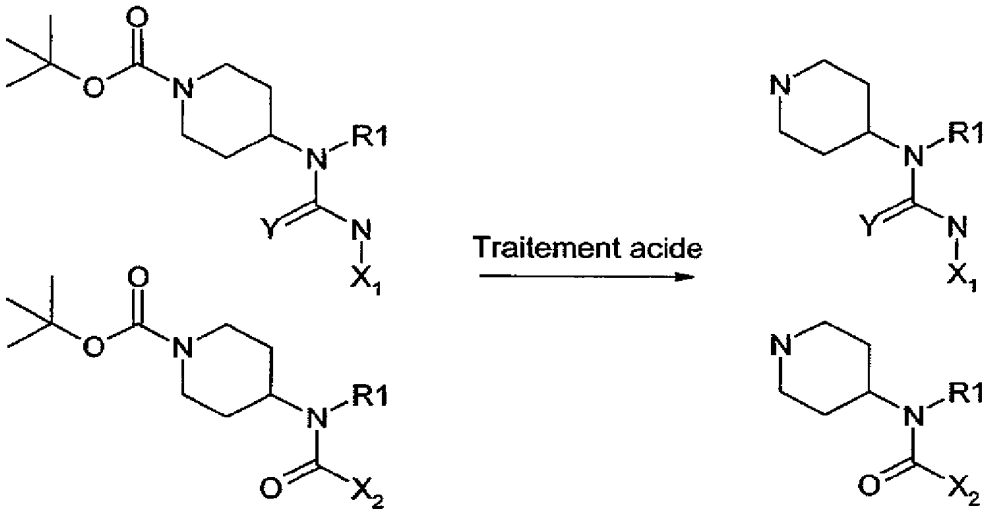


où le groupe protecteur (GP) représente H ou *tert*-butyloxycarbonyle.

A3) Synthèses de pipéridines 4-aminodisubstituées

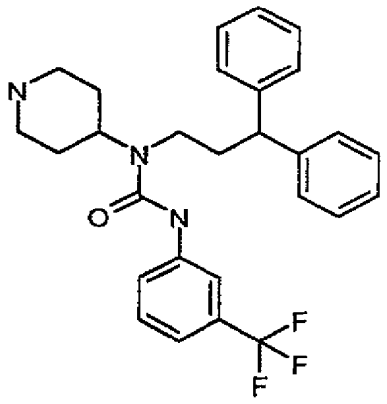
La synthèse des pipéridines 4-aminodisubstituées selon l'invention, peut s'effectuer par traitement acide des composés N-Boc précédemment décrits, suivant le schéma réactionnel suivant :

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Procédure générale : deux méthodes ont été utilisées pour effectuer la déprotection en milieu acides des urées, thiourées et amides précédemment décrits. La première consiste à dissoudre le composé dans du dichlorométhane et additionner l'acide trifluoroacétique (5 à 20 éq.) tandis que dans la seconde une solution d'acide chlorhydrique dilué dans des solvants tels que l'acétate d'éthyle, le dioxane ou le diéthyléther (5 à 20 éq.) est utilisée. La réaction est agitée 1 à 4 heures à température ambiante. Dans certains cas, du dichlorométhane est ajouté et la phase organique est lavée avec une solution saturée de bicarbonate de sodium, séchée sur sulfate de magnésium, filtrée et concentrée sous vide pour isoler la base libre.

Exemple A3 : Urée de N-(3,3-diphénylpropyl)-N-(4-pipéridinyl)-N'-[3-(trifluoro méthyl)phényl] ($C_{28}H_{30}F_3N_3O$, M = 481,57)



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A une solution de carboxylate de *tert*-butyl4-((3,3-diphénylpropyl){[3-(trifluorométhyl)anilino]carbonyl}amino)-1-pipéridine (600 mg, 1,04 mmol) dans le dichlorométhane est ajouté 1,6 ml (21 mmol, 20 éq.) d'acide trifluoroacétique. La réaction est agitée 90 minutes puis concentrée. Du dichlorométhane est ajouté et la phase organique est lavée avec une solution saturée de bicarbonate de sodium, séchée sur sulfate de magnésium, filtrée et concentrée sous vide pour isoler 490 mg (rdt = 98 %) d'une mousse blanche.

RMN ^{1}H (CD_3OD, 400 MHz) δ : 7,7 (s, 1H) ; 7,55 (d, 1H) ; 7,44 (t, 1H) ; 7,28 (m, 9H) ; 7,18 (m, 2H) ; 4,05 (m, 2H) ; 3,26 (m, 2H) ; 3,11 (d, J = 10,8Hz, 2H) ; 2,7 (td, J = 2,4 et 12,4Hz, 2H) ; 2,38 (q, J = 8Hz, 2H) ; 1,76 (d, J = 10Hz, 2H) ; 1,63 (qd, J = 4 et 12,4Hz, 2H). SM/CL : m/z = 482,2 (M+H).

Une série de 4-aminopipéridines a été synthétisée selon cette procédure. Les radicaux R_1, X_1 et X_2 que l'on peut envisager sont ceux déjà illustrés aux points A1 et A2 ci-dessus.

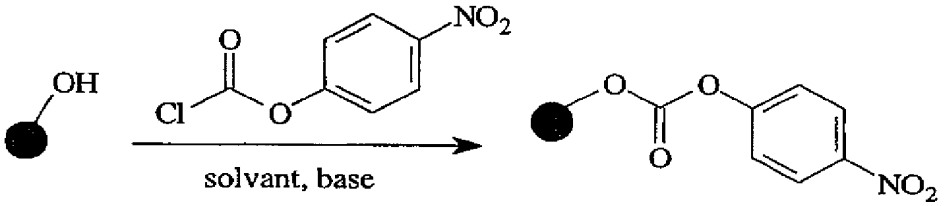
B) Synthèse en phase solide de 4-aminopipéridines

Des 4-aminopipéridines ont été préparées par synthèse en phase solide en partant de la résine de Wang.

B1) Préparation de la résine

B1a) Préparation de la résine carbonate de *p*-nitrophényle de Wang

Elle s'effectue selon le schéma suivant



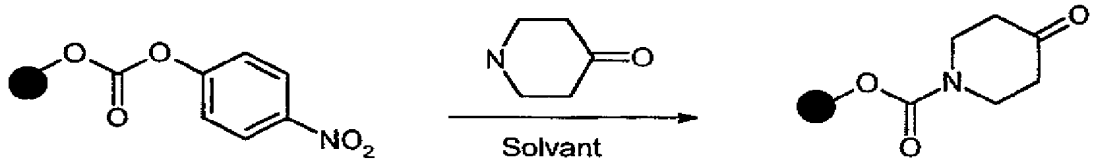
Cette résine a été préparée à partir de la résine de Wang (fournie par Bachem ou Novabiochem) avec des taux de charge supérieurs à 0.89mmol/g, suivant la procédure décrite dans la littérature (Bunin, B.A. *The Combinatorial Index*, Academic Press, **1998**, p. 62-63 ; Dressman, B.A. ; Spangle, L.A. ; Kaldor, S.W.

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Tetrahedron Lett. **1996**, *37*, 937-940 ; Hauske, J.R. ; Dorff, P. *Tetrahedron Lett.* **1995**, *36*, 1589-1592; Cao, J. ; Cuny, G.D. ; Hauske, J.R. *Molecular Diversity* **1998**, *3*, 173-179) : de la N-méthylmorpholine ou de la pyridine et du chloroformiate de 4-nitrophényle sont successivement additionnés à la résine de Wang prégonflée dans du dichlorométhane ou du tétrahydrofurane à température ambiante. Le mélange est agité toute la nuit. La résine est lavée avec du tétrahydrofurane, du diéthyléther et du dichlorométhane puis séchée *in vacuo* à 50° C toute la nuit.

B1b) Préparation de la résine carbamate de pipéridone

Elle s'effectue selon le schéma suivant



Au chlorhydrate hydraté de pipéridone dilué dans de la diméthylformamide est ajoutée de la triéthylamine (1 éq.) et du tamis moléculaire. Le mélange est chauffé jusqu'à dissolution complète de la cétone. Cette solution est ajoutée à la résine carbonate de *p*-nitrophényle de Wang (0,05 éq.) prégonflée dans la diméthylformamide. Après 24 à 72 heures d'agitation à température ambiante, la résine est filtrée puis lavée plusieurs fois avec de la diméthylformamide, du tétrahydrofurane, du diéthyléther et du dichlorométhane.

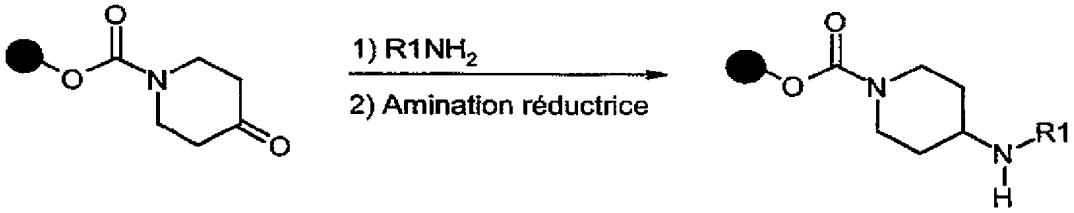
Préparation 2

2,5 g de la résine carbonate de *p*-nitrophényle de Wang (taux de charge de 0,88 mmol/g, 2,2 mmol) est prégonflée dans 100 ml de diméthylformamide. Dans le même temps, 6,7 g (44 mmol, 20 éq.) de chlorhydrate hydraté de pipéridone, 4,45 g (44 mmol, 20 éq.) de triéthylamine et trois spatules de tamis moléculaire sont chauffés dans 100 ml de diméthylformamide jusqu'à dissolution complète. La solution jaunâtre est versée chaude sur la résine et le mélange agité 40 heures à température ambiante. La résine est filtrée puis lavée avec de la diméthylformamide, du tétrahydrofurane, du diéthyléther et du dichlorométhane (3 fois chaque solvant) puis séchée sous vide. 2,4 g de résine jaune pale sont isolés avec un taux de charge de 0,88 mmol/g calculé d'après l'analyse élémentaire de l'azote.

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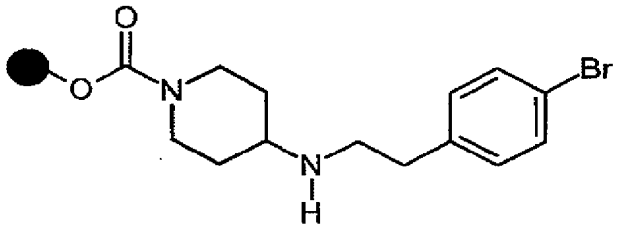
B2) Amination réductrice sur support solide

Elle s'effectue selon le schéma



La procédure générale est la suivante : à la résine cétonique prégonflée dans le triméthylorthoformiate (TMOF) est ajoutée l'amine primaire (5 à 10 éq.) puis le mélange est soniqué. On ajoute ensuite le complexe de borane pyridine (8 M, 5 à 10 éq.) et le mélange est agité 12 à 72 heures. La résine est filtrée, lavée avec des solvants tels que le dichlorométhane, la diméthylformamide et le tétrahydrofurane puis séchée sous vide (Pelter, A.; Rosser, R.M. *J. Chem. Soc. Perkin Trans I* **1984**, 717-720; Bomann, M.D.; Guch, I.C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995-5996; Khan, N.M.; Arumugam, V.; Balasubramanian, S. *Tetrahedron Lett.* **1996**, *37*, 4819-4822).

Préparation 3



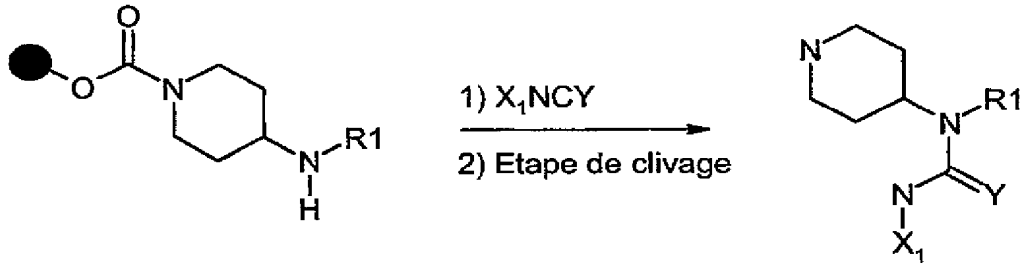
300 mg (taux de charge de 0,88 mmol/g, 0,27 mmol) de résine cétonique sont prégonflés dans le TMOF. On ajoute ensuite la 4-bromophénéthylamine (540 mg, 420 µl, 2,7 mmol, 10 éq.) puis le complexe de borane pyridine (8 M, 338 µl, 2,7 mmol, 10 éq.). Le mélange est agité 56 heures à température ambiante. La résine est filtrée, rincée successivement avec du dichlorométhane, du diméthylformamide, du tétrahydrofurane et du dichlorométhane puis séchée sous vide. 340 mg de résine jaune pale sont ainsi obtenus avec un taux de charge de 0,81 mmol/g calculé d'après l'analyse élémentaire de l'azote.

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B3) Fonctionalisation

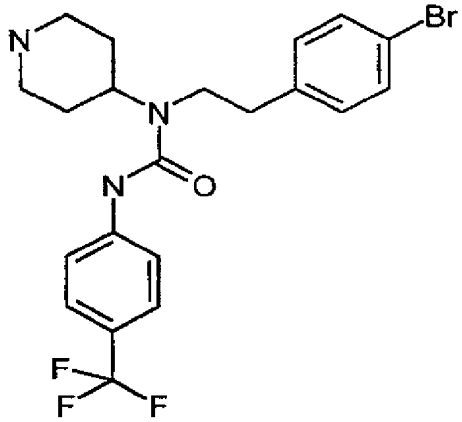
B3a) Fonctionalisation avec des isocyanates ou des isothiocyanates

Elle s'effectue selon le schéma



La procédure générale est la suivante : la résine "amine secondaire" est prégonflée dans un solvant tel que le dichlorométhane ou le diméthylformamide avant l'addition d'isocyanate ou d'isothiocyanate (3 à 10 éq.). Le mélange est agité 1 à 24 heures à température ambiante. La résine est alors filtrée, lavée avec des solvants tels que le dichlorométhane, le diméthylformamide et le tétrahydrofurane puis séchée sous vide. Le clivage de la résine s'effectue en présence d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique et une agitation de 30 minutes à 4 heures. La résine est rincée au dichlorométhane puis le filtrat est concentré sous vide. Dans certains cas le filtrat est redissout dans du dichlorométhane puis désalifié avec une solution saturée de carbonate de sodium. La phase organique est évaporée sous vide pour donner la base libre.

Exemple B3a : Urée de N-(4-bromophénéthyl)-N-(4-pipéridinyl)-N'-[4-(trifluorométhyl) phényl] ($C_{21}H_{23}BrF_3N_3O$, M = 470,3)

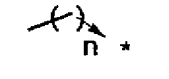


55 mg (50 µmol) de la résine (voir préparation 3) sont prégonflés dans du dichlorométhane anhydre. On ajoute ensuite le 4-trifluorophénylisocyanate (28 mg, 150 µmol, 3 éq.) et le tout est agité toute la nuit. La résine est filtrée, rincée au tétrahydrofurane, au diméthylformamide, au tétrahydrofurane puis au dichlorométhane avant d'être séchée sous vide. On agite ensuite 1,5 heure en présence de 800 µl d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique. La résine est filtrée et rincée au dichlorométhane, le filtrat est concentré, redilué dans du dichlorométhane et lavé avec une solution saturée de bicarbonate de sodium. 6 mg d'une huile brune (rdt = 25 %) sont ainsi isolés.

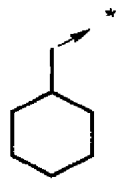
RMN ^1H (CD_3OD, 400 MHz) δ: 7,53 (m, 4H); 7,44 (d, J = 6,8Hz, 2H); 7,21 (d, J = 8,4Hz, 2H); 4,1 (m, 1H); 3,53 (t, J = 7,2Hz, 2H); 3,12 (d, J = 12,8Hz, 2H); 2,89 (t, J = 8Hz, 2H); 2,7 (m, 2H); 1,73 (m, 4H). SM/CL : m/z = 472,2 (M+H).

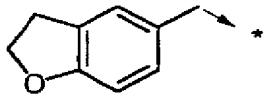
Une série d'urées (Y = O) et de thiourées (Y = S) a été synthétisée selon cette procédure. Les radicaux R_1 que l'on peut envisager sont les suivants :

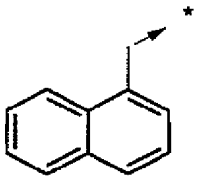
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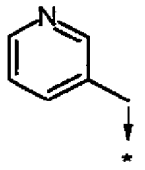


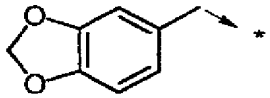
n = 0 -15

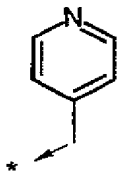


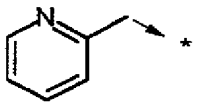


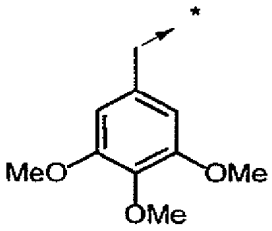


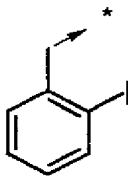




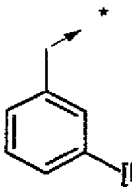




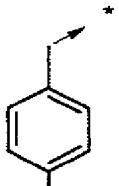




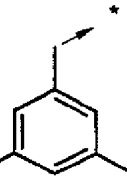
[H, F, Br, Cl, OMe, SMe, OEt, CF_3, OCF_3, Ph, Me]



[F, Cl, OMe, Me, CF_3, OCF_3, Ph]

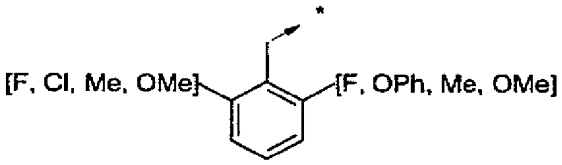


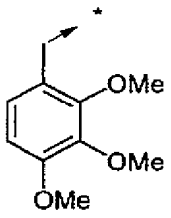
[F, Cl, OMe, SMe, Me, CF_3, OCF_3, Ph, OPh]

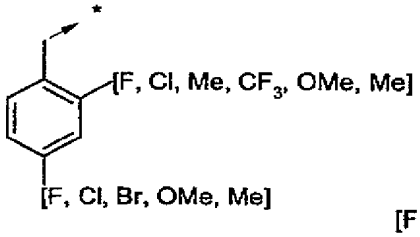


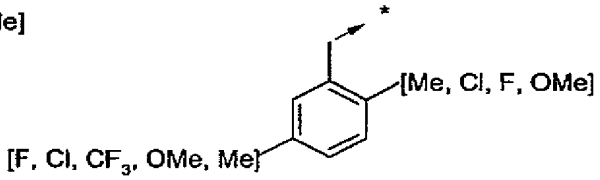
[Cl, F, OMe, Me, CF_3] [Cl, F, CF_3, OMe, Me]

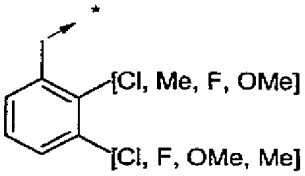
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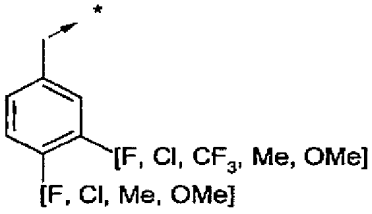




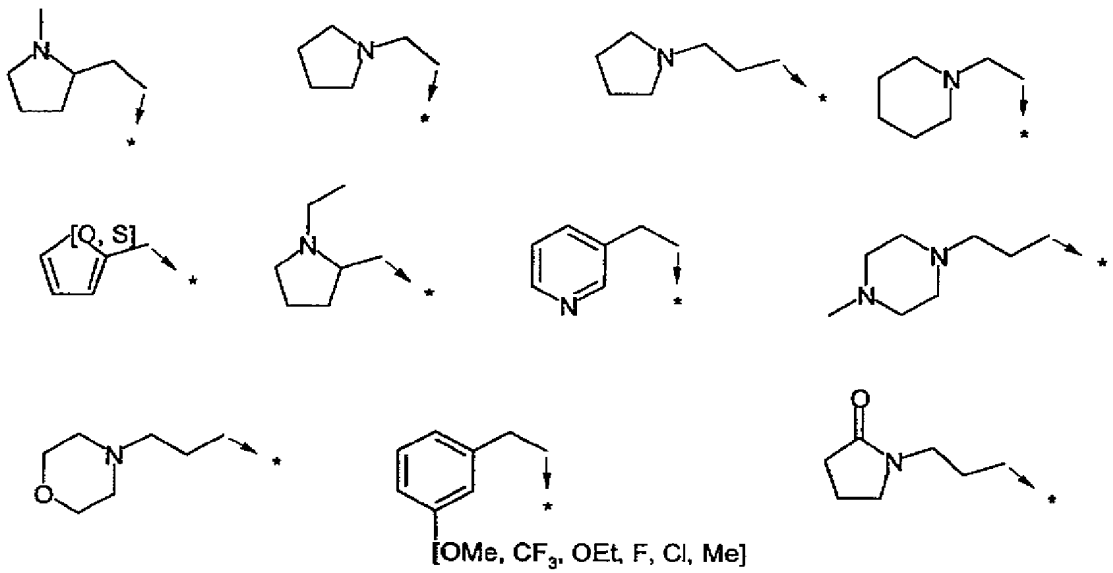




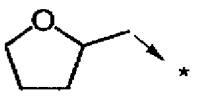




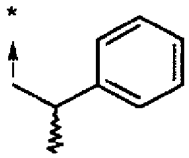
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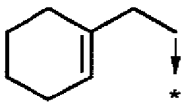


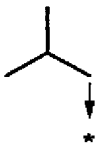
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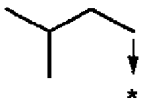


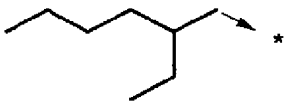


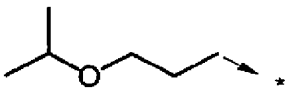


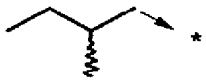


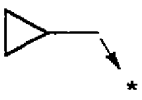


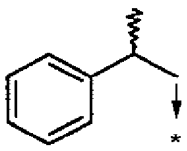


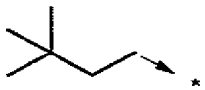




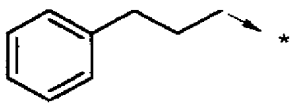


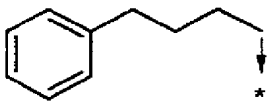


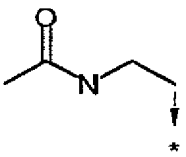


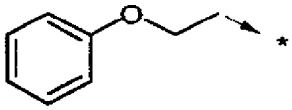


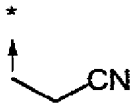


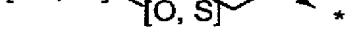


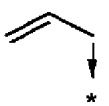


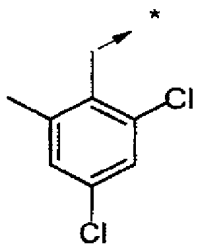


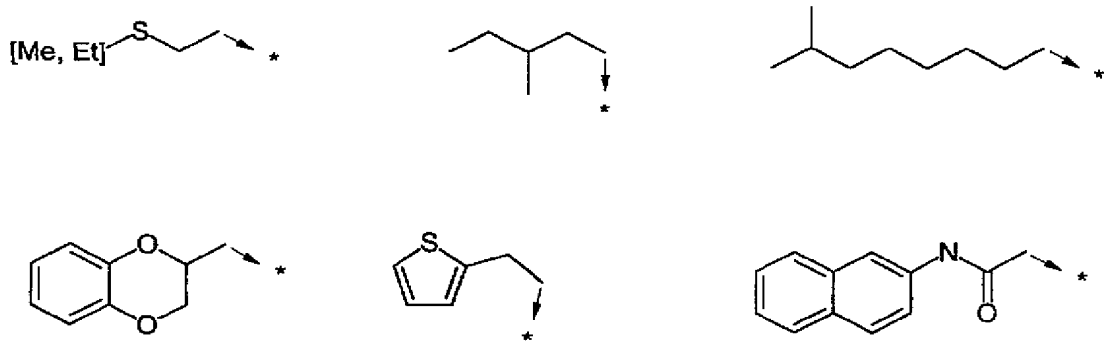








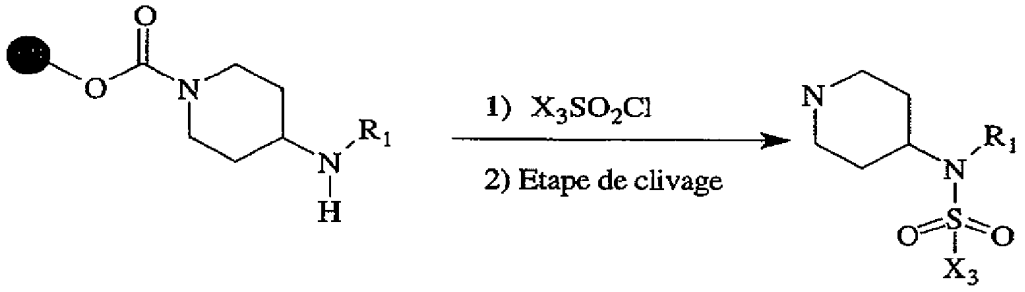




Les radicaux X_1 que l'on peut envisager sont ceux illustrés au point A ci-dessus.

B3b) Fonctionalisation avec des chlorures de sulfonyles

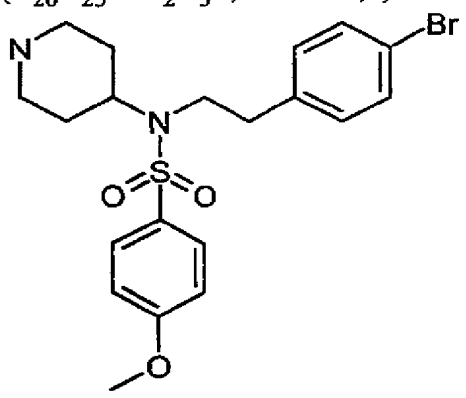
Elle s'effectue selon le schéma suivant



Procédure générale : la résine "amine secondaire" est prégonflée dans des solvants comme le dichlorométhane, le diméthylformamide ou le tétrahydrofurane. Puis le chlorure de sulfonyle (5 à 10 éq.) et la triéthylamine (6 à 12 éq.) sont ajoutés et le mélange agité de 12 à 24 heures à température ambiante. La résine est filtrée, lavée avec des solvants tels que le dichlorométhane, le diméthylformamide et le tétrahydrofurane, puis séchée sous vide. On agite ensuite la résine de 1 à 4 heures en présence d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique. La résine est rincée au dichlorométhane puis le filtrat est concentré sous vide. Dans certains cas le filtrat est redissout dans du dichlorométhane puis désalifié avec une solution saturée de carbonate de sodium. La phase organique est évaporée sous vide pour donner la base libre.

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Exemple B3b : Sulfonamide de N-(4-bromophénéthyl)-4-méthoxy-N-(4-pipéridinyl) phényle ($C_{20}H_{25}BrN_2O_3S$, M = 453,4)

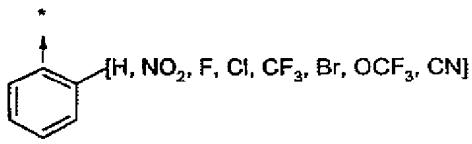


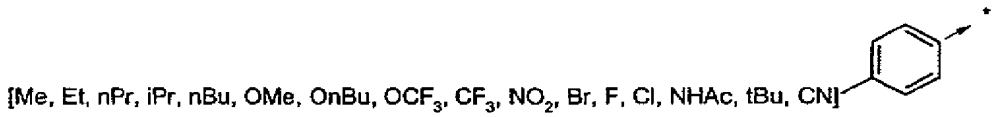
55 mg (50 µmol) de résine (voir préparation 3) sont prégonflés dans du dichlorométhane anhydre. On ajoute ensuite la triéthylamine (42 µl, 300 µmol, 6 éq.) puis le chlorure de 4-méthoxybenzène sulfonyle (51,5 mg, 250 µmol, 5 éq.) et le tout est agité toute la nuit. La résine est filtrée, rincée au tétrahydrofurane, au diméthylformamide, au tétrahydrofurane puis au dichlorométhane avant d'être séchée sous vide. On répète la réaction une seconde fois pour avoir une substitution complète. On ajoute 800 µl d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique et on agite 1,5 heure à température ambiante. La résine est filtrée et rincée au dichlorométhane. Le filtrat est concentré, redilué dans du dichlorométhane et lavé avec une solution saturée de bicarbonate de sodium. 14 mg d'une huile brune (rdt = 63%) ont ainsi été isolés.

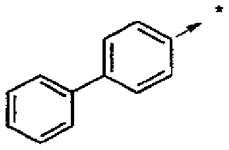
RMN ^1H (CD_3OD, 400 MHz) δ : 7,8 (dd, J = 2,8 et 10Hz, 2H); 7,44 (dd, J = 1,2 et 6,8Hz, 2H); 7,17 (d, J = 8,4Hz, 2H); 7,07 (dd, J = 3,2 et 10Hz, 2H); 3,87 (s, 3H, OCH_3); 3,72 (m, 1H); 3,3 (m, 2H); 3,04 (d, J = 12,8Hz, 2H); 2,92 (t, J = 8,4Hz, 2H); 2,6 (t, J = 12,4Hz, 2H); 1,58 (m, 2H); 1,47 (d large, J = 10Hz, 2H). SM/CL : m/z = 455 (M+H).

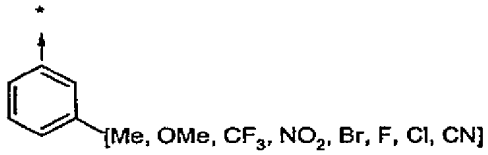
Une série de sulfonamides a été synthétisée selon cette procédure. Les radicaux R_1 que l'on peut envisager sont ceux illustrés aux points A et B3a ci-dessus. Les radicaux X_3 que l'on peut envisager sont les suivants :

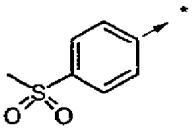
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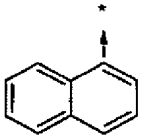

[H, NO2, F, Cl, CF3, Br, OCF3, CN]

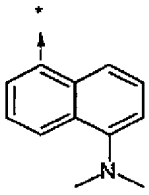

[Me, Et, nPr, iPr, nBu, OMe, OnBu, OCF3, CF3, NO2, Br, F, Cl, NHAc, tBu, CN]

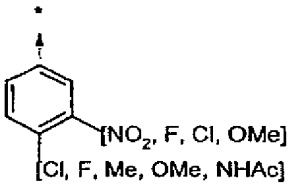


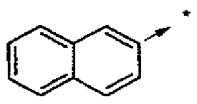

[Me, OMe, CF3, NO2, Br, F, Cl, CN]

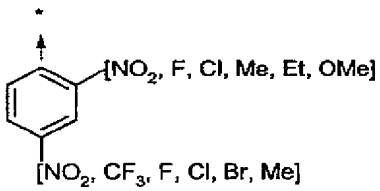


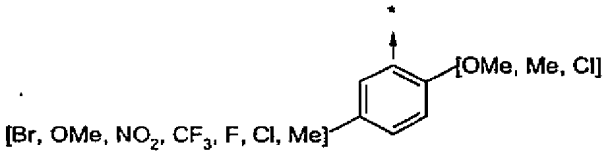


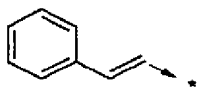


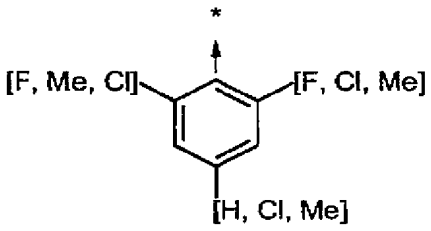

[NO2, F, Cl, OMe]
[Cl, F, Me, OMe, NHAc]

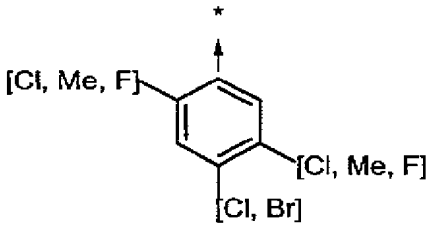


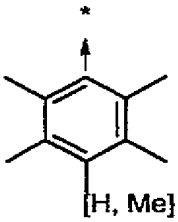

[NO2, F, Cl, Me, Et, OMe]
[NO2, CF3, F, Cl, Br, Me]

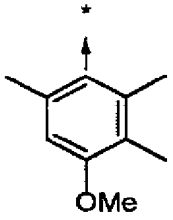

[OMe, Me, Cl]
[Br, OMe, NO2, CF3, F, Cl, Me]

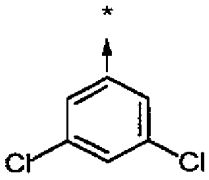


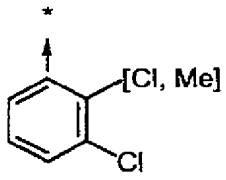


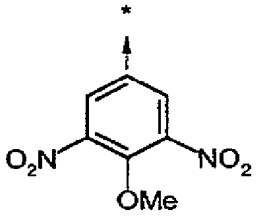


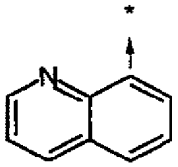


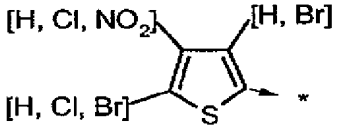


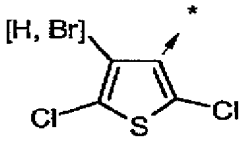


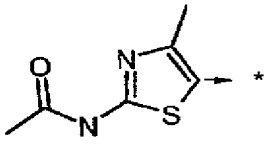


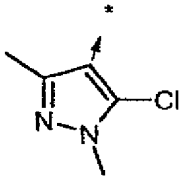


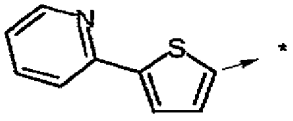


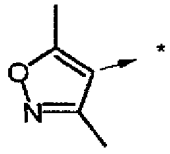


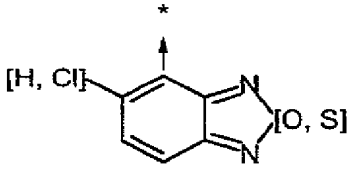


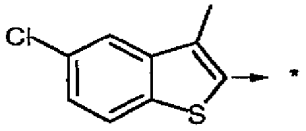


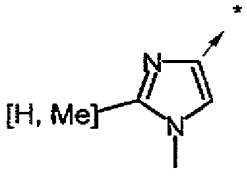


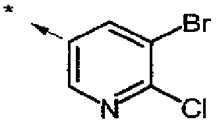




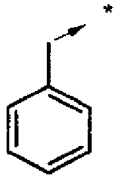


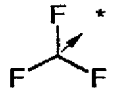








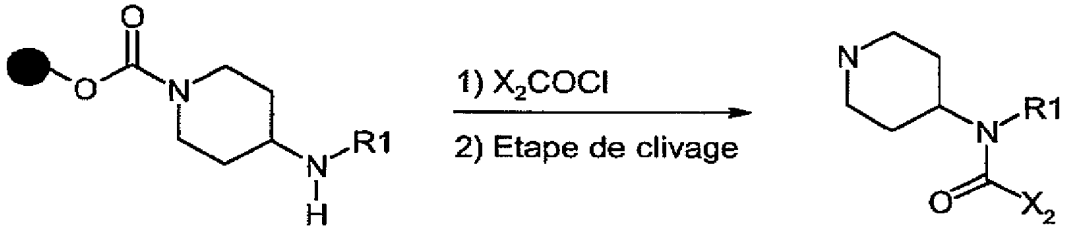




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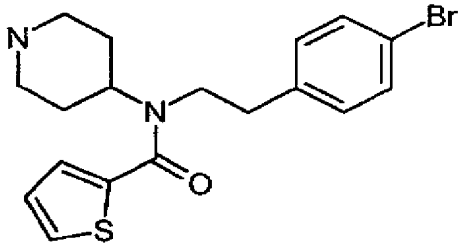
B3c) Fonctionalisation avec des chlorures d'acides

Elle s'effectue selon le schéma suivant



Procédure générale : la résine "amine secondaire" est prégonflée dans des solvants comme le dichlorométhane, le diméthylformamide ou le tétrahydrofurane. Puis le chlorure d'acide (5 à 10 éq.) et la triéthylamine (6 à 12 éq.) sont ajoutés et le mélange agité de 12 à 24 heures à température ambiante. La résine est filtrée, lavée avec des solvants tels que le dichloromethane, le diméthylformamide et le tétrahydrofurane, puis séchée sous vide. On agite ensuite la résine de 1 à 4 heures en présence d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique. La résine est rincée au dichlorométhane puis le filtrat est concentré sous vide. Dans certains cas le filtrat est redissout dans du dichlorométhane puis désalifié avec une solution saturée de carbonate de sodium. La phase organique est évaporée sous vide pour donner la base libre.

Exemple B3c : Carboxamide de N-(4-bromophénéthyl)-N-(4-pipéridinyl)-2-thiophène ($C_{18}H_{21}BrN_2OS$, M = 393,3)



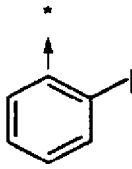
55 mg (50 µmol) de la résine (voir préparation 3) sont prégonflés dans du tétrahydrofurane anhydre. On ajoute ensuite la triéthylamine (42 µl, 300 µmol, 6 éq.) puis le chlorure de 2-thiophène carbonyle (37 mg, 250 µmol, 5 éq.) et le tout est agité toute la nuit. La résine est filtrée, rincée au tétrahydrofurane, au diméthylformamide, au tétrahydrofurane puis au dichlorométhane avant d'être séchée sous vide. On ajoute 800 µl d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique et on agite 1,5 heure à température ambiante. La résine est filtrée et rincée au

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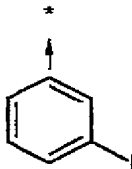
dichlorométhane. Le filtrat est concentré, redilué dans du dichlorométhane et lavé avec une solution saturée de bicarbonate de sodium. pour obtenir 10 mg d'une huile brune (rdt = 50 %).

RMN ^{1}H (CD_3OD, 400 MHz) δ : 7,64 (dd, J = 0,8 et 4,8Hz, 1H); 7,44 (d, J = 8,4Hz, 2H); 7,36 (d, J = 3,6Hz, 1H); 7,14 (m, 3H); 4,11 (m, 1H); 3,61 (t, J = 8Hz, 2H); 3,09 (d, J = 12Hz, 2H); 2,92 (m, 2H); 2,54 (m, 2H); 1,82 (m, 2H); 1,7 (m, 2H). SM/CL : m/z = 393,1 (M+H).

Une série d'amides a été synthétisée selon cette procédure. Les groupes R_1 envisagés sont ceux illustrés aux points A et B3a ci-dessus. Les groupes X_2 sont illustrés ci-dessous.



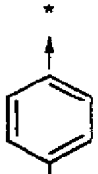
[H, F, Cl, Br, I, CN, OCF_3, NO_2, Me, CF_3, OMe]



[F, Cl, Br, CF_3, Me, CN, NO_2, OMe, OEt]

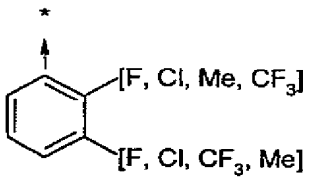


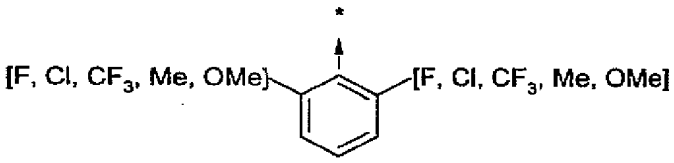
[F, Cl, Br, I, NMe_2, CO_2Me, OCF_3, OnAm, NO_2, CN, tBu, Me, Et, nPr, nBu, nAm]

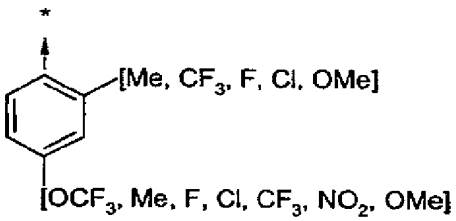


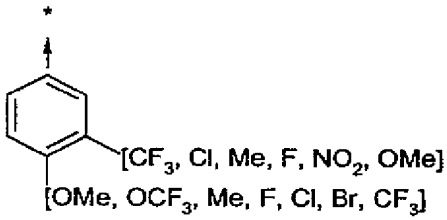
[OMe, OEt, Ph, CF_3, OnBu, SCF_3]

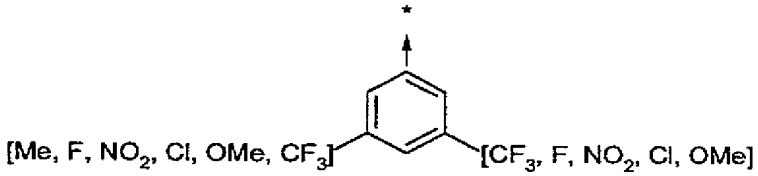
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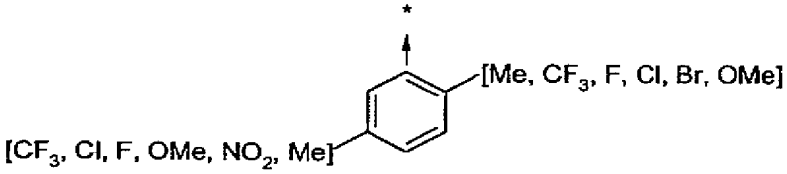

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[F, Cl, CF_3, Me]

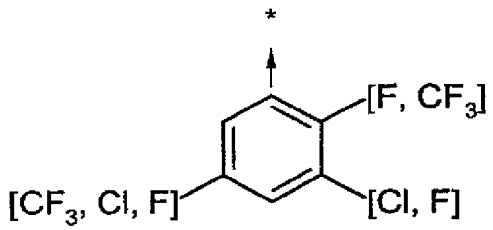

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[F, Cl, CF_3, Me, OMe]

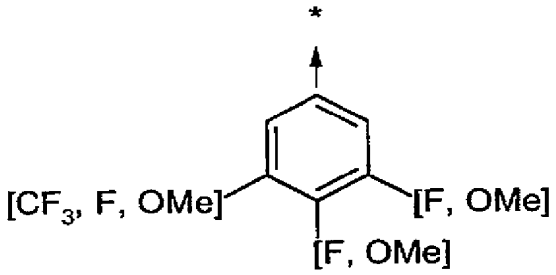

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[OCF_3, Me, F, Cl, CF_3, NO_2, OMe]

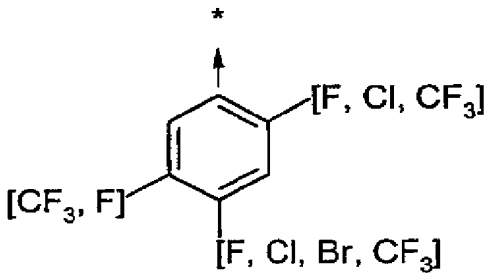

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[CF_3, Cl, Me, F, NO_2, OMe]
[OMe, OCF_3, Me, F, Cl, Br, CF_3]

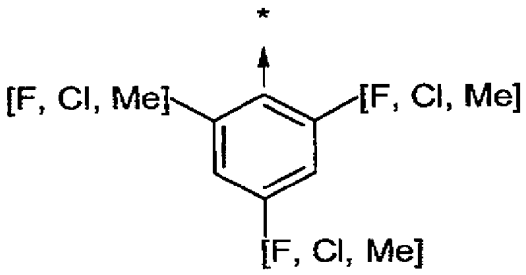

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[CF_3, F, NO_2, Cl, OMe]

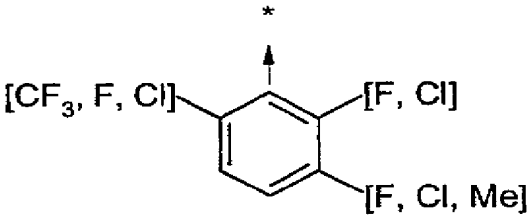

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[Me, CF_3, F, Cl, Br, OMe]
[CF_3, Cl, F, OMe, NO_2, Me]

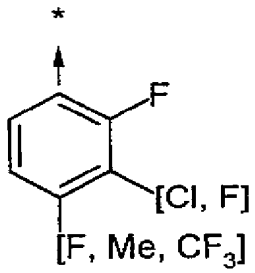

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[F, CF3]
[CF3, Cl, F]
[Cl, F]

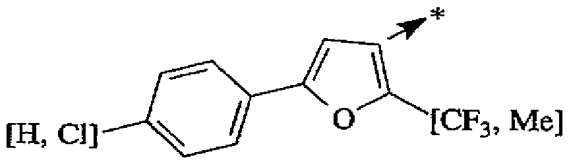

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[F, OMe]
[F, OMe]

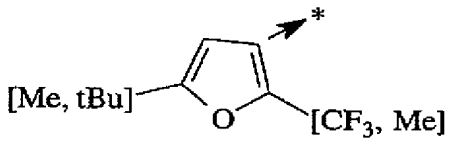

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[CF3, F]
[F, Cl, Br, CF3]

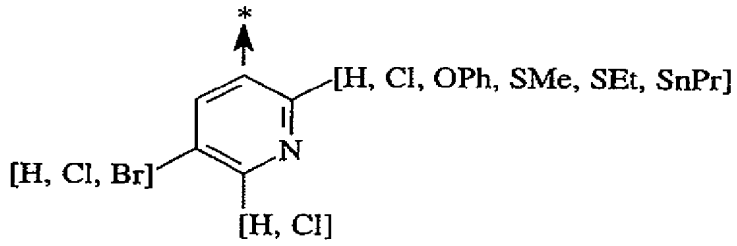

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[F, Cl, Me]
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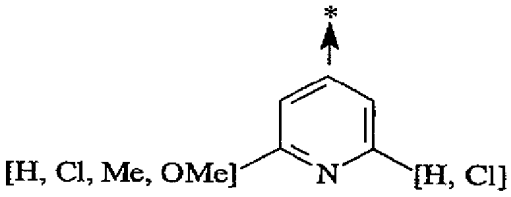

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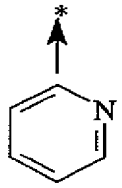

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F
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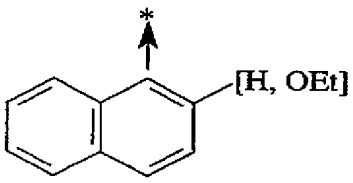


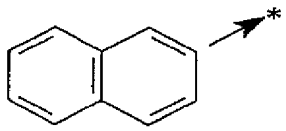


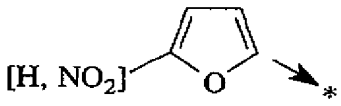


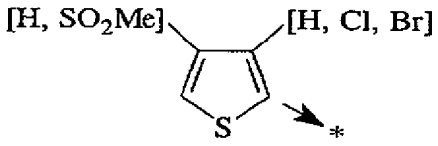


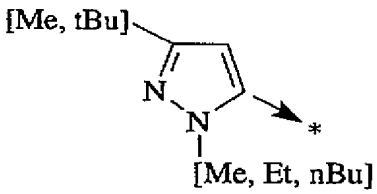




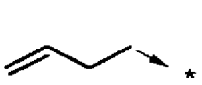


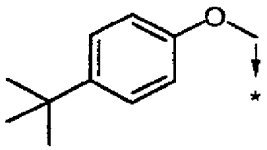




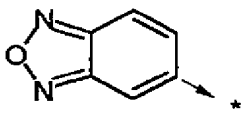


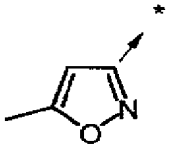
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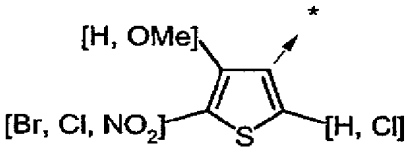


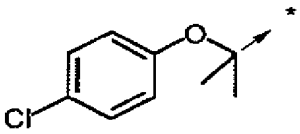


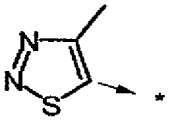


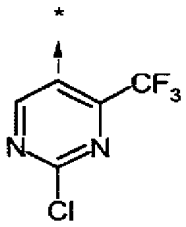


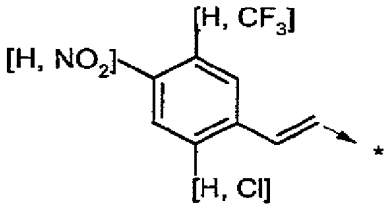


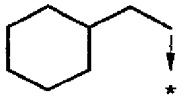


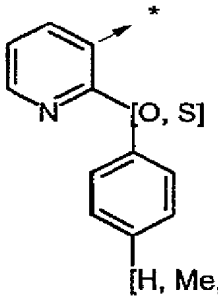




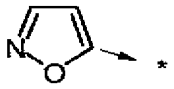


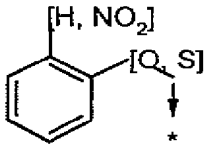




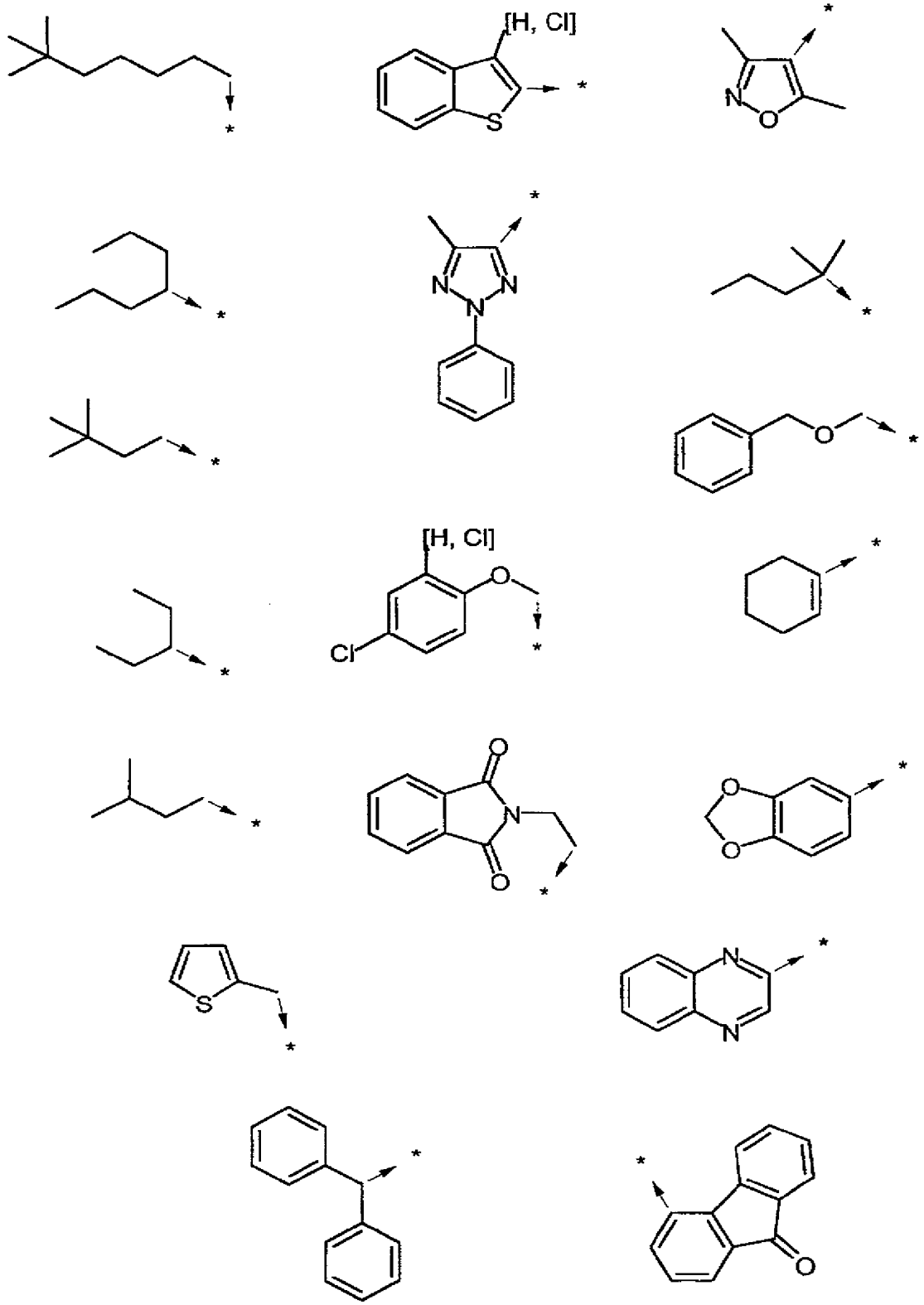


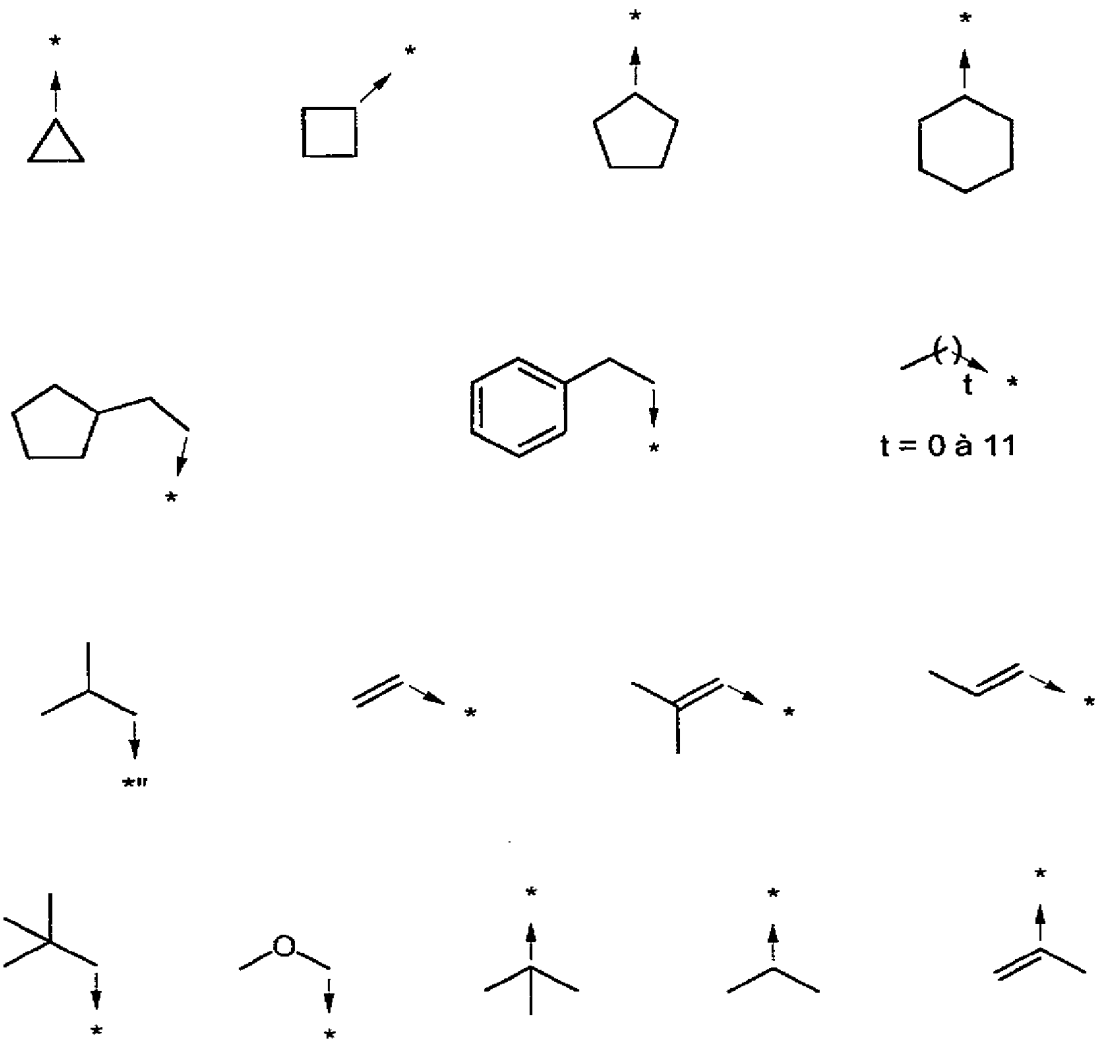






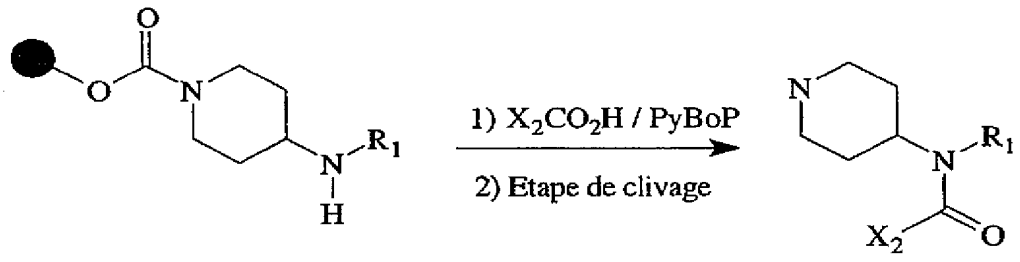
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[H, Cl]
N
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[H, Cl]
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N
N



B3d) Fonctionalisation avec des acides carboxyliques

Elle s'effectue selon la procédure décrite dans la littérature (Kobayashi, S ; Aoki, Y., *J. Comb. Chem.* **1999**, *1*, 371-372) suivant le schéma :



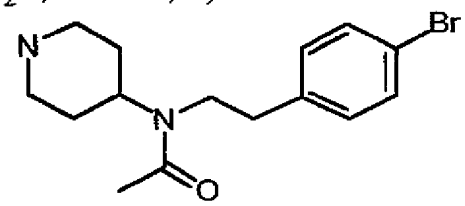
Procédure générale : la résine "amine secondaire" est prégonflée dans des solvants comme le dichlorométhane, le diméthylformamide ou le tétrahydrofurane. Puis

NSDOCID: <FR___2802206A1_I_>

l'acide carboxylique (3 à 5 éq.), l'hexafluorophosphate de benzo-triazol-1-yl-oxy-tris-pyrrolidino phosphonium (PyBoP, 3 à 5 éq.) et la diisopropyléthylamine (6 à 10 éq.) sont ajoutés et le mélange agité 24 heures à température ambiante. La résine est filtrée, lavée avec des solvants tels que le dichlorométhane, le diméthylformamide et le tétrahydrofurane, puis séchée sous vide. On agite ensuite la résine de 1 à 4 heures en présence d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique. La résine est rincée au dichlorométhane puis le filtrat est concentré sous vide. Dans certains cas le filtrat est redissout dans du dichlorométhane puis désalifié avec une solution saturée de carbonate de sodium. La phase organique est évaporée sous vide pour donner la base libre.

Exemple B3d : Acétamide de N-[2-(4-bromophényl)éthyl]-N-(4-pipéridinyl)

($C_{15}H_{21}BrN_2O$, M = 325,25)



55 mg (50 µmol) de la résine (voir préparation 3) sont prégonflés dans de la diméthylformamide anhydre. On ajoute ensuite l'acide acétique (8,8 mg, 150 µmol, 3 éq.), le PyBoP (76 mg, 150 µmol, 3 éq.) puis la diisopropyléthylamine (38 mg, 300 µmol, 6 éq.) et le tout est agité toute la nuit. La résine est filtrée, rincée au diméthylformamide, au tétrahydrofurane puis au dichlorométhane avant d'être séchée sous vide. On ajoute 800 µl d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique et on agite 1,5 heure à température ambiante. La résine est filtrée et rincée au dichlorométhane. Le filtrat est concentré, redilué dans du dichlorométhane et lavé avec une solution saturée de bicarbonate de sodium pour obtenir 11 mg d'une huile brune (rdt = 68 %).

RMN ^1H (CD_3OD, 400 MHz) δ : 7,44 (m, 2H); 7,20 (m, 2H); 4,05 (m,1H); 3,45 (m, 2H); 3,10 (m, 2H); 2,83 (m, 2H); 2,64 (m, 2H); 2,13 (s,3H) ; 1,73 (m, 4H). SM/CL : m/z = 325,2 (M+H).

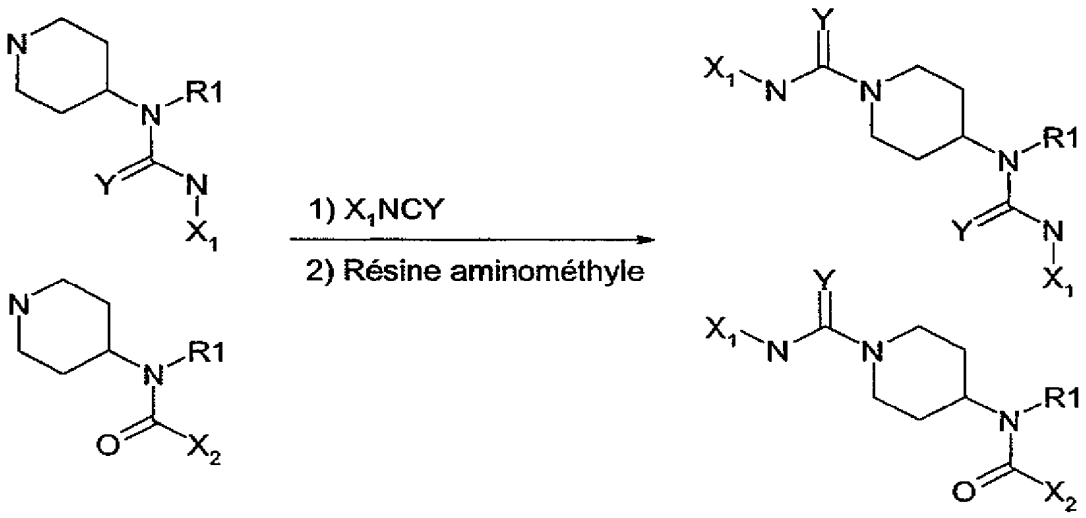
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Une série d'amides a été synthétisée selon cette procédure. Les groupes R_1 envisagés sont ceux illustrés aux points A et B3a ci-dessus. Les groupes X_2 sont illustrés au point A ci-dessus.

C) Fonctionalisation de la partie pipéridine en solution

C1) Obtention de pipéridine avec R_3= -C(Y)NHX_1

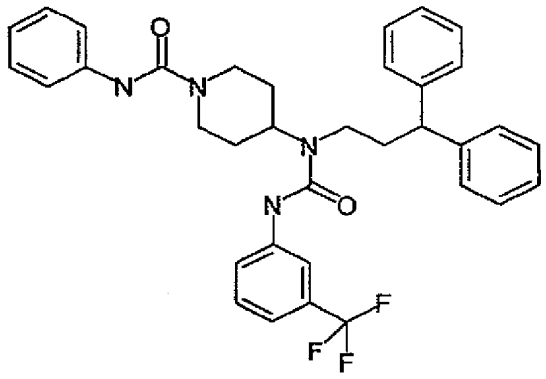
Elle s'effectue selon le schéma



Procédure générale : à la pipéridine sous forme de base libre diluée dans du dichloromethane, est ajouté un isocyanate ou isothiocyanate (1,1 à 1,5 éq.). Le mélange est agité d'une à 18 heures à température ambiante. La résine aminométhyle (0,2 à 1 éq.) est ajoutée et le mélange à nouveau agité de 2 à 18 heures. Dans certains cas, de la résine échangeuse d'ions telle que IRA68 ou SAX est ajoutée. Les résines sont filtrées et le filtrat concentré. Dans certains cas, le produit est dissout dans du dichlorométhane ou de l'acétate d'éthyle puis filtré sur une catouche de gel de silice ou d'alumine basique (500 mg, Interchim).

Exemple C1 : Carboxamide de 4-((3,3-diphénylpropyl){[3-(trifluorométhyl)anilino] carbonyl}amino)-N-phényl-1-pipéridine ($C_{35}H_{35}F_3N_4O_2$, M = 600,68)

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L'urée de N-(3,3-diphénylpropyl)-N-(4-pipéridinyl)-N'-[3-(trifluorométhyl)phényl] (24 mg, 0,05 mmol) est dissoute dans du dichlorométhane. Le phénylisocyanate (9 mg, 0,075 mmol, 1,5 éq.) est ajouté et le mélange agité pendant 2,5 heures. La résine aminométhyle (0,02 mmol) est ajoutée et la réaction à nouveau agitée toute la nuit. La résine est filtrée, rincée avec du dichlorométhane et le filtrat concentré. L'huile obtenue est passée sur une cartouche de gel de silice en éluant avec un mélange équimolaire d'heptane et d'acétate d'éthyle pour obtenir après concentration 12 mg (rdt = 40 %) d'une huile jaune.

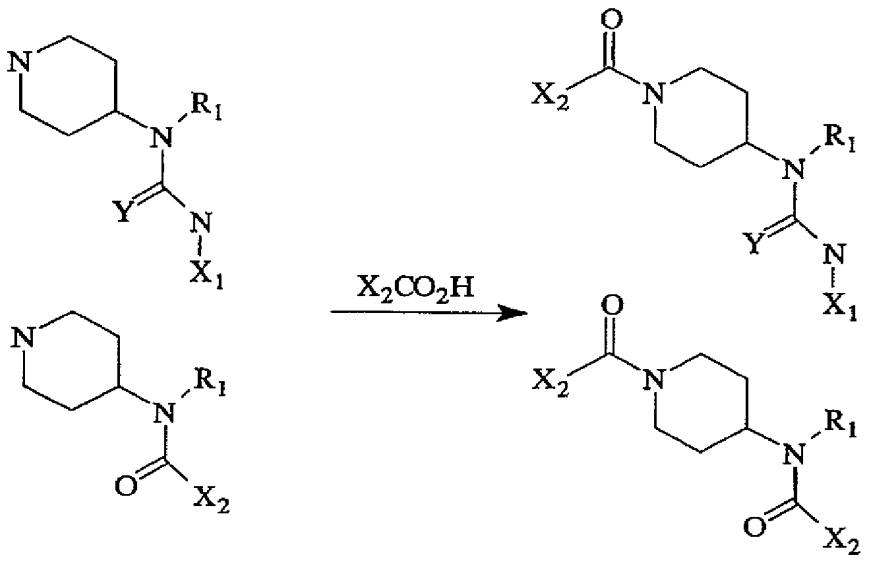
RMN ^1H (CD_3OD, 400 MHz) δ : 7,72 (s, 1H) ; 7,58 (d, 1H) ; 7,44 (m, 1H) ; 7,38 (m, 2H) ; 7,29 (m, 12H) ; 7,12 (m, 2H) ; 7,07 (m, 1H) ; 4,2 (d, J = 12,4Hz, 3H) ; 3,21 (t, J = 8Hz, 2H) ; 2,9 (t, J = 12,4Hz, 2H) ; 2,38 (q, J = 8Hz, 2H) ; 1,73 (d, J = 10Hz, 2H) ; 1,54 (qd, J = 3,6 et 12Hz, 2H). SM/CL : m/z = 601,4 (M+H).

Une série d'urées (Y = O) et de thiourées (Y = S) ont été synthétisées selon cette procédure. Les groupes R_1, X_1 et X_2 que l'on peut envisager, sont ceux illustrés aux points ci-dessus (A et B3a), A, et (A et B3c) respectivement.

C2) Fonctionalisation avec des acides carboxyliques

Elle s'effectue selon le schéma suivant

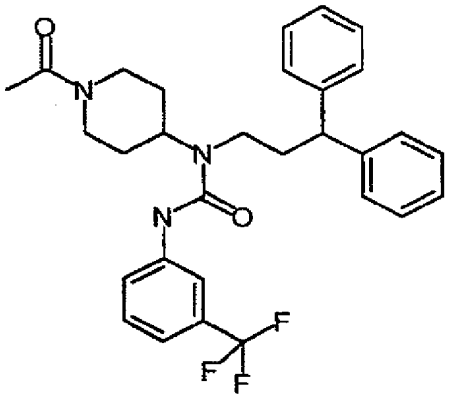
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Procédure générale: la résine P-EDC (1,3 à 3 éq.) est prégonflée dans du dichlorométhane anhydre. L'acide carboxylique (1,1 à 2,5 éq.) est dissout dans un solvant anhydre tel que le dichlorométhane, le diméthylformamide ou le tétrahydrofurane et ajouté à la résine. Ce mélange est agité de 5 à 30 minutes à température ambiante. On ajoute alors à ce mélange la pipéridine 4-aminodisubstituée, sous forme de base libre, en solution dans un solvant anhydre tel que le dichlorométhane, le diméthylformamide ou le tétrahydrofurane et on agite le tout à température ambiante de 1 à 18 heures. Dans certains cas, de la résine échangeuse d'ions telle que IRA68 ou SAX est ajoutée et le mélange agité à nouveau à température ambiante de 1 à 18 heures. Les résines sont filtrées sur fritté, sur cartouche de résine échangeuse d'ions SAX (500 mg, Interchim) ou sur cartouche d'alumine basique (500 mg, Interchim).

Exemple C2 : Urée de N-(1-acétyl-4-pipéridinyl)-N-(3,3-diphénylpropyl)-N'-[3-(trifluorométhyl) phényl] ($C_{30}H_{32}F_3N_3O_2$, M = 523,60)

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117 mg (175 µmol, 3,5 éq.) de résine P-EDC est prégonflée dans 1,5 ml de dichlorométhane anhydre. L'acide acétique (7,5 mg, 125 µmol, 2,5 éq.) est ajouté et le mélange agité 10 minutes. Puis l'urée de N-(3,3-diphénylpropyl)-N-(4-pipéridinyl)-N'-[3-(trifluorométhyl)phényl] (24,3 mg, 50 µmol) est ajoutée à son tour et le mélange agité toute la nuit. La résine est filtrée et le filtrat concentré. L'huile obtenue est passée sur une cartouche de gel de silice en éluant avec un mélange équimolaire d'heptane et d'acétate d'éthyle pour obtenir après concentration 16mg (rdt = 62 %) d'une mousse blanche.

RMN ^1H (CD_3OD, 400 MHz) δ : 7,71 (s, 1H) ; 7,58 (d, J = 8,4Hz, 1H) ; 7,43 (t, J = 8Hz, 1H) ; 7,28 (m, 9H) ; 7,17 (m, 2H) ; 4,56 (dd, J = 2 et 11,2Hz, 1H) ; 4,17 (m, 1H) ; 3,96 (t, J = 7,6Hz, 1H) ; 3,88 (d, J = 12Hz, 1H) ; 3,19 (q, J = 4 et 8Hz, 2H) ; 3,1 (t, J = 12Hz, 1H) ; 2,58 (t, J = 12Hz, 1H); 2,37 (m, 2H); 2,06 (s, 3H, CH_3) ; 1,72 (t, J = 14,4Hz, 2H) ; 1,43 (qd, J = 4 et 12,4Hz, 2H).

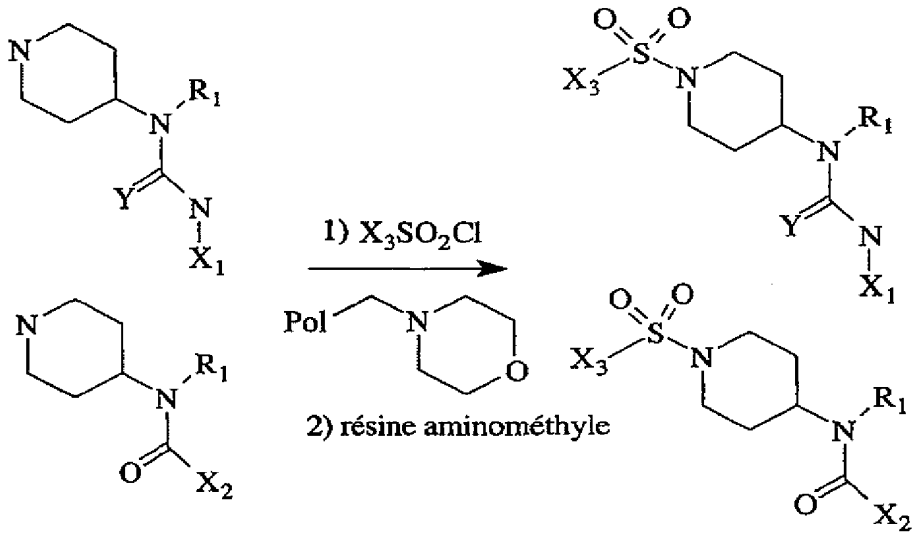
SM/CL : m/z = 524,3 (M+H).

Une série d'amides a été synthétisée selon cette procédure. Les groupes R_1, X_1 et X_2 que l'on peut envisager, sont ceux illustrés aux points (A et B3a), A, (A et B3c) respectivement.

C3) Fonctionalisation avec des chlorures de sulfonyles

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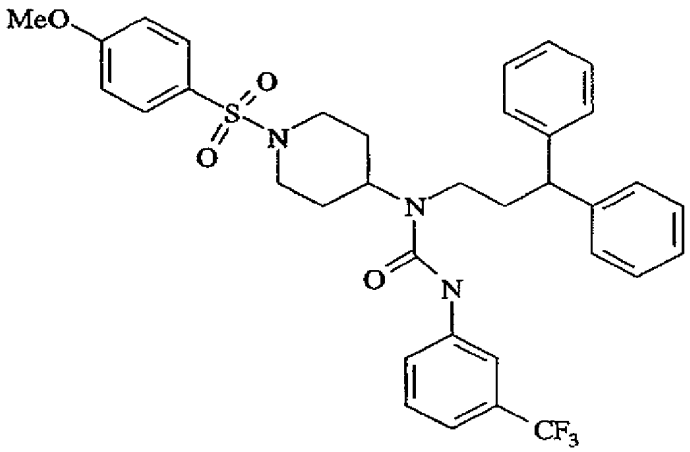
Elle s'effectue selon le schéma suivant



Procédure générale: la résine morpholinométhyle (Novabiochem, 2 à 3 éq.) est prégonflée dans des solvants anhydres tels que le dichlorométhane, le diméthylformamide ou le tétrahydrofurane. Le chlorure de sulfonyle (1,1 à 2 éq.) dissout dans des solvants anhydres tels que le dichlorométhane, le diméthylformamide ou le tétrahydrofurane est ajouté, suivi de la pipéridine 4-aminodisubstituée. Le mélange est agité de 16 à 48 heures. La résine aminométhyle (0,1 à 1,5 éq.) est ajoutée et la réaction agitée toute la nuit. Dans certains cas, de la résine échangeuse d'ions telle que IRA68 ou SAX est ajoutée et le mélange agité à température ambiante de 1 à 18 heures. Les résines sont filtrées sur fritté, sur cartouche de résine échangeuse d'ions SAX (500 mg, Interchim) ou sur cartouche d'alumine basique (500 mg, Interchim).

Exemple C3 : Urée de N-(3,3-diphénylpropyl)-N-{1-[(4-méthoxyphényl)sulfonyl]-4-pipéridinyl}-N'-[3-(trifluorométhyl)phényl] ($C_{35}H_{36}F_3N_3O_4S$, M = 651,75)

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27,5 mg (100 µmol, 2 éq.) de résine morpholinométhyle est prégonflée dans du tétrahydrofurane anhydre, on ajoute alors le chlorure de 4-méthoxyphénylsulfonyle (15,5 mg, 0,075 mmol, 1,5 éq.) puis l'urée de N-(3,3-diphénylpropyl)-N-(4-pipéridinyl)-N'-[3-(trifluorométhyl)phényl] (24,3 mg, 0,05 mmol). Le mélange est agité toute la nuit. Les résines aminométhyle (20 mg) et échangeuse d'ions SAX sont ajoutées et le mélange est agité toute la nuit. Les résines sont filtrées et rincées au dichlorométhane. L'huile obtenue après évaporation est passée sur une cartouche de gel de silice (500 mg, Interchim) en éluant avec de l'acétate d'éthyle pour obtenir après concentration 18 mg (rdt = 56 %) d'un solide blanc.

RMN ^1H (CD_3OD, 400 MHz) δ : 7,71 (d, J = 9,2Hz, 2H) ; 7,65 (s, 1H) ; 7,51 (d, 1H) ; 7,41 (t, J = 7,6Hz, 1H) ; 7,29 (m, 9H) ; 7,20 (m, 2H) ; 7,11 (dd, J = 1,6 et 6,8Hz, 2H) ; 3,88 (s, 3H, OCH_3) ; 3,77 (d, J = 12,4Hz, 2H) ; 3,16 (t, J = 8Hz, 2H) ; 2,33 (m, 4H) ; 1,71 (d, J = 10Hz, 2H); 1,62 (qd, J = 4 et 12Hz, 2H) ; 1,3 (m, 2H). SM/CL : m/z = 652,4 (M+H).

Une série de sulfonamides a été synthetisée selon cette procédure. Les groupes R_1, X_1, X_2 et X_3 que l'on peut envisager, sont ceux illustrés aux points (A et B3a), A, (A et B3c) et B3b respectivement.

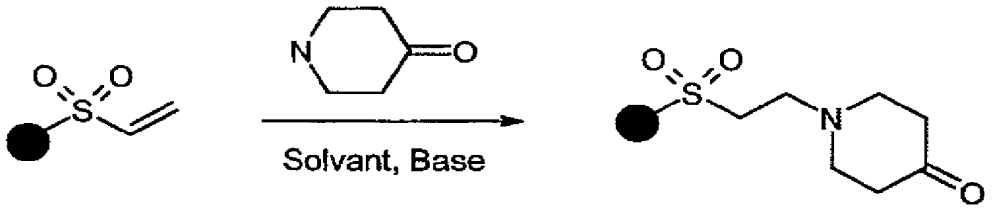
D) Synthèse de pipéridines tri-substituées en phase solide

Elle s'effectue à partir de la résine vinyle sulfone (Kroll, F.E.K. ; Morphy, R. ; Rees, D. ; Gani, D. *Tetrahedron Lett.* **1997**, *38*, 8573-8576; Brown, A.R. *J. Comb. Chem.* **1999**, *1*, 283-285) selon le schéma suivant :

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D1) Préparation de la résine

Elle s'effectue selon le schéma suivant :



Au chlorhydrate hydraté de pipéridone dilué dans la diméthylformamide est ajoutée de la triéthylamine (1 éq.). Le mélange est chauffé jusqu'à dissolution complète de la cétone. Cette solution est ajoutée à la résine vinyle sulfone (0,05 éq.) prégonflée dans la diméthylformamide. Après 24 à 72 heures d'agitation à température ambiante, la résine est filtrée puis lavée plusieurs fois avec de la diméthylformamide, du tétrahydrofurane, du diéthyléther et du dichlorométhane.

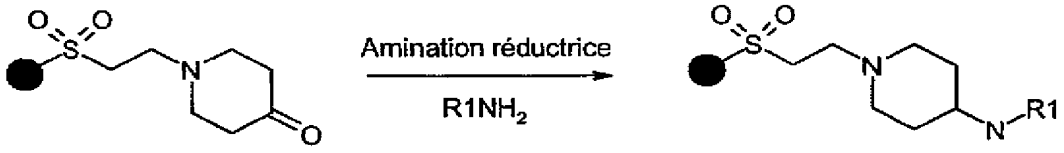
Préparation 4

1,5 g de la résine vinyle sulfone (Novabiochem, taux de charge de 1 mmol/g, 1,5 mmol) est prégonflée dans 50 ml de diméthylformamide. Dans le même temps, 2,3 g (15 mmol, 10 éq.) de chlorhydrate hydraté de pipéridone et 1,8 g (15 mmol, 10 éq.) de triéthylamine sont chauffés dans 100 ml de diméthylformamide jusqu'à dissolution complète. La solution jaunâtre est versée chaude sur la résine et le mélange agité 24 heures à température ambiante. La résine est filtrée puis lavée avec de la diméthylformamide, du tétrahydrofurane, du diéthyléther et du dichlorométhane (3 fois chaque solvant) puis séchée sous vide. 1,7 g de résine jaune pale sont isolés avec un taux de charge de 1mmol/g calculé d'après l'analyse élémentaire de l'azote.

D2) Amination réductrice sur support solide

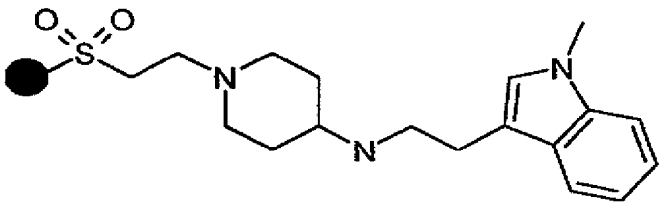
Elle s'effectue selon la procédure décrite dans la littérature (Pelter, A.; Rosser, R.M. *J. Chem. Soc. Perkin Trans I* **1984**, 717-720; Bomann, M.D.; Guch, I.C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995-5996; Khan, N.M.; Arumugam, V.; Balasubramanian, S. *Tetrahedron Lett.* **1996**, *37*, 4819-4822) suivant le schéma :

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Procédure générale : A la résine cétonique prégonflée dans le triméthylorthoformiate (TMOF) est ajoutée l'amine primaire (5 à 10 éq.) puis le mélange est soniqué. On ajoute ensuite le complexe de borane pyridine (8 M, 5 à 10 éq.) et le mélange est agité 12 à 72 heures. La résine est filtrée, lavée avec des solvants tels que le dichlorométhane, la diméthylformamide, le méthanol et le tétrahydrofurane puis séchée sous vide.

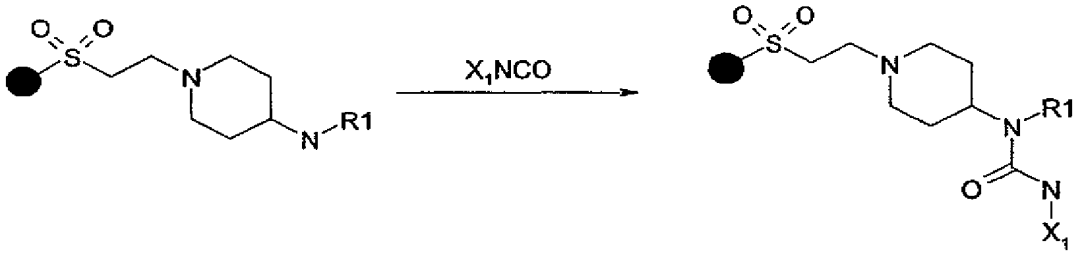
Préparation 5



1 g (taux de charge de 1mmol/g, 1mmol) de résine cétonique sont prégonflés dans le TMOF. On ajoute ensuite la 2-(1-méthyl-1*H*-indol-3-yl)éthylamine (1,01 g, 10 mmol, 10 éq.) puis le complexe de borane pyridine (8M, 1,25 ml, 10 mmol, 10 éq.). Le mélange est agité 48 heures à température ambiante. La résine est filtrée, rincée successivement avec du dichlorométhane, du diméthylformamide, du méthanol, du tétrahydrofurane et du dichlorométhane puis séchée sous vide. 1,05 g de résine jaune pale sont ainsi obtenus avec un taux de charge de 0,91 mmol/g calculé d'après l'analyse élémentaire de l'azote.

D3) Fonctionalisation de l'amine secondaire

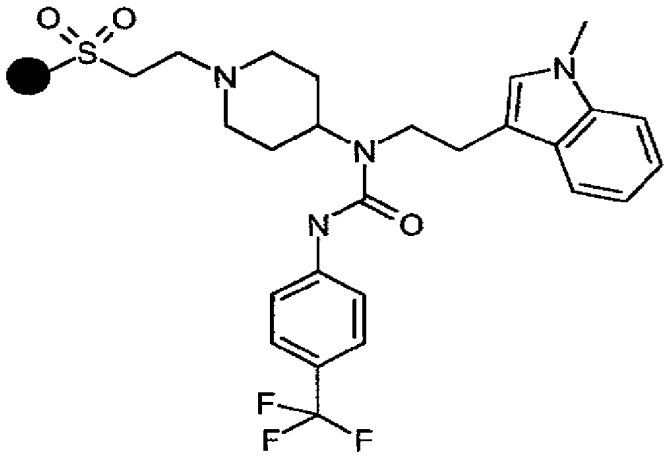
D3a) Fonctionalisation avec des isocyanates



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Procédure générale : la résine "amine secondaire" est prégonflée dans un solvant tel que le dichlorométhane ou la diméthylformamide avant l'addition de l'isocyanate (3 à 10 éq.). Le mélange est agité 1 à 24 heures à température ambiante. La résine est alors filtrée, lavée avec des solvants tels que le dichlorométhane, la diméthylformamide et le tétrahydrofurane puis séchée sous vide.

Préparation 6



55 mg (50 µmol) de la résine (voir préparation 5) sont prégonflés dans du dichlorométhane anhydre. On ajoute ensuite le 4-trifluorophénylisocyanate (28 mg, 150 µmol, 3 éq.) et le tout est agité 2 heures à température ambiante. La résine est filtrée, rincée au tétrahydrofurane, au diméthylformamide, au tétrahydrofurane puis au dichlorométhane avant d'être séchée sous vide.

D3b) Fonctionalisation avec des chlorures de sulfonyles

Le mode opératoire de fonctionalisation est idendique à celui exposé au point B3b.

D3c) Fonctionalisation avec des chlorures d'acides

Le mode opératoire de fonctionalisation est identique à celui exposé au point B3c.

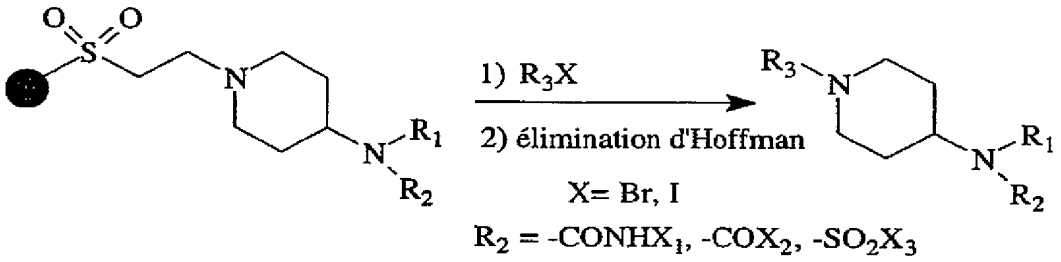
D3d) Fonctionalisation avec des acides carboxyliques

Le mode opératoire de fonctionalisation est identique à celui exposé au point B3d.

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D4) Etape de clivage

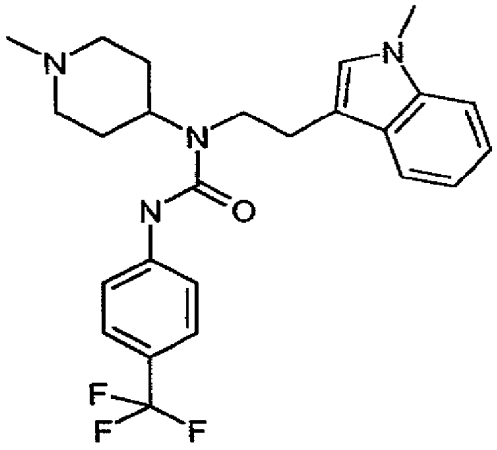
L'étape de clivage décrite ci-dessous est valable quelque soit la fonctionalisation opérée au préalable sur l'amine secondaire :



Procédure générale : La résine disubstituée est gonflée dans des solvants tels que le dichlorométhane, la diméthylformamide ou le tétrahydrofurane puis est ajouté l'halogénure R_3X dans lequel R_3 a la signification indiquée précédemment et X représente un atome d'halogène (5 éq.) et le mélange agité toute la nuit à une température comprise entre 20 et 60° C. La résine est filtrée, rincée avec des solvants tels que la diméthylformamide, le tétrahydrofurane, le méthanol et le dichlorométhane puis séchée sous vide. La résine est regonflée dans le dichlorométhane et de la résine échangeuse d'ions basiques (Ouyang, X.; Armstrong, R.W.; Murphy, M.M. *J. Org. Chem.* **1998**, *63*, 1027-1032) est ajoutée. Agiter le tout 48 heures à température ambiante. Les résines sont filtrées, rincées au dichlorométhane et le filtrat concentré sous vide.

Exemple D4 : Urée de *N*-[2-(1-méthyl-1*H*-indol-3-yl)éthyl]-*N*-(1-méthyl-4-pipéridinyl)-*N'*-[4-(trifluorométhyl)phényl] ($C_{25}H_{29}F_3N_4O$, M = 458,5)

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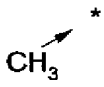


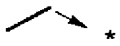
55 mg (50 µmol) de la résine urée sont gonflés dans de la diméthylformamide puis 35 mg (250 µmol, 5 éq.) de iodométhane sont ajoutés et le mélange agité 18 heures à température ambiante. La résine est filtrée, rincée avec de la diméthylformamide, du tétrahydrofurane, du méthanol et du dichlorométhane puis séchée sous vide. La résine est regonflée dans du dichlorométhane puis environ 100 mg de résine amberlite IRA68 sont ajoutés et le mélange agité 48 heures. Les résines sont filtrées, rincées avec du dichlorométhane et le filtrat concentré pour donner 18 mg (rdt = 78 %) d'une huile incolore.

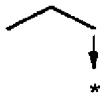
RMN ^{1}H (CD_3OD, 400 MHz) δ: 7,65 (m, 2H); 7,40 (m, 2H); 7,31 (m, 1H); 7,20 (t, 1H) ; 7,10 (m, 1H); 7,06 (m, 2H) ; 4,04 (m, 1H); 3,68 (s, 3H) ; 3,60 (t, 2H); 3,04 (t, 2H); 2,94 (m, 2H); 2,29 (s, 3H); 2,14 (m, 2H) ; 1,91 (m, 2H) ; 1,76 (m, 2H). SM/CL : m/z = 459,3 (M+H).

Pour les groupes R_1, X_1, X_2 et X_3 tels qu'illustrés aux points A et B ci-dessus, les groupes R_3 que l'on peut envisager pour la synthèse de 4-aminopipéridines trisubstitutées selon la procédure ci-dessus, sont les suivants :

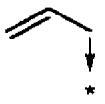
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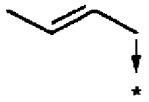

CH3

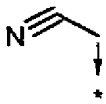




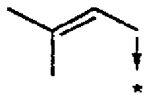


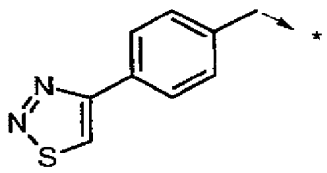


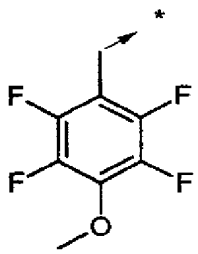


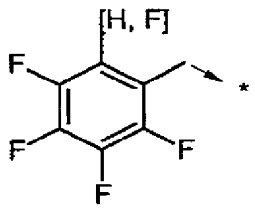

N

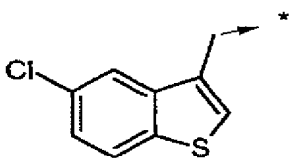


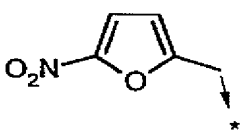


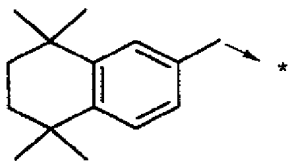

N
N
S

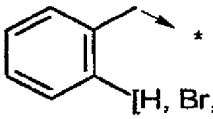

F
F
F
F
O


[H, F]
F
F
F
F

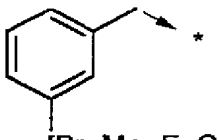

Cl
S


O2N
O

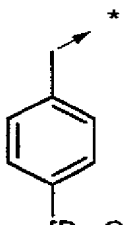




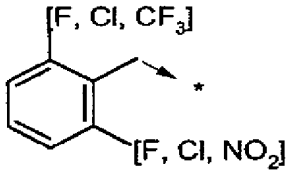
[H, Br, Me, F, Cl, CN, NO_2, CF_3, Ph, $OCHF_2$, I, OCF_3, SCF_3, $SCHF_2$]



[Br, Me, F, Cl, I, CF_3, CN, NO_2, OCF_3, OMe, $OCHF_2$, SCF_3, $SCHF_2$, CO_2Me]

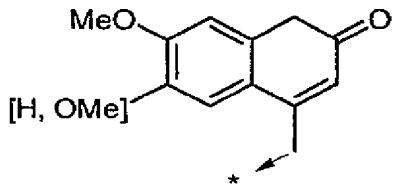


[Br, Cl, tBu, Me, F, CF_3, CN, NO_2, Ph, CO_2Me, OCF_3, $OCHF_2$, SCF_3, SO_2Me, I]



[F, Cl, CF_3]

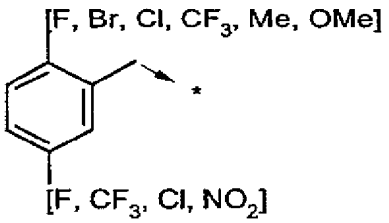
[F, Cl, NO_2]



MeO

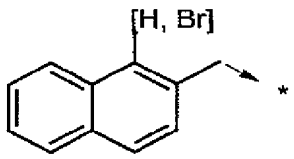
O

[H, OMe]

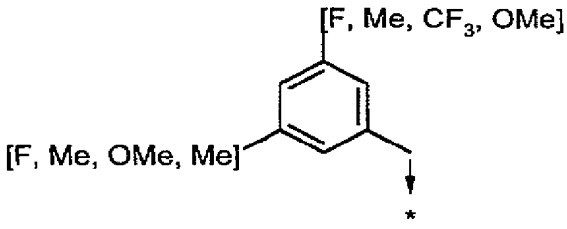


[F, Br, Cl, CF_3, Me, OMe]

[F, CF_3, Cl, NO_2]



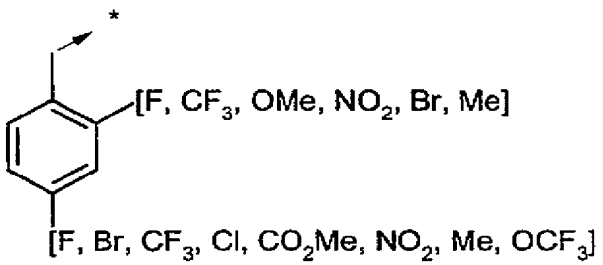
[H, Br]

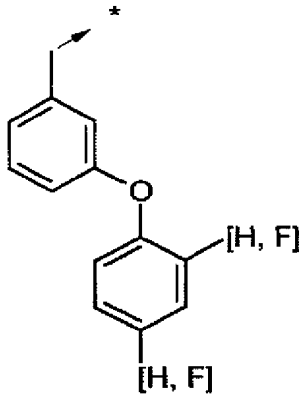


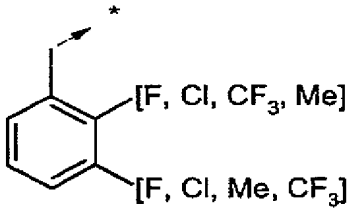
[F, Me, CF_3, OMe]

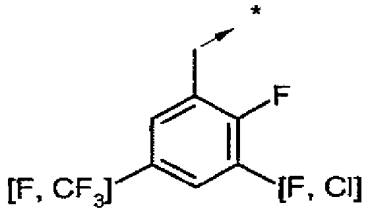
[F, Me, OMe, Me]

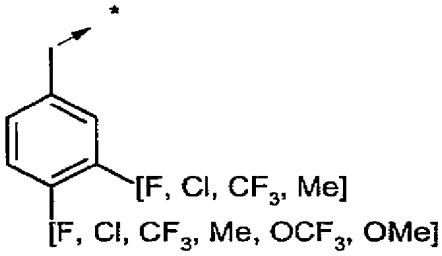
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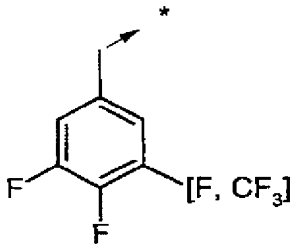

*
[F, CF3, OMe, NO2, Br, Me]
[F, Br, CF3, Cl, CO2Me, NO2, Me, OCF3]

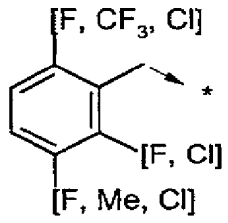

*
O
[H, F]
[H, F]

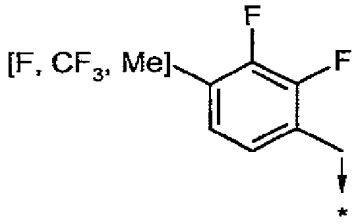

*
[F, Cl, CF3, Me]
[F, Cl, Me, CF3]

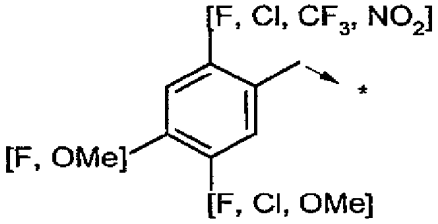

*
F
[F, CF3]
[F, Cl]

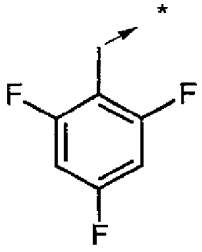

*
[F, Cl, CF3, Me]
[F, Cl, CF3, Me, OCF3, OMe]

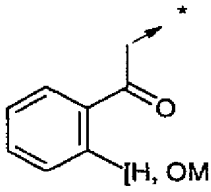

*
F
[F, CF3]
F


[F, CF3, Cl]
*
[F, Cl]
[F, Me, Cl]

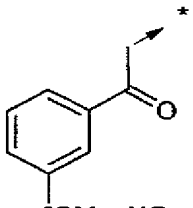

F
[F, CF3, Me]
F
*


[F, Cl, CF3, NO2]
*
[F, OMe]
[F, Cl, OMe]

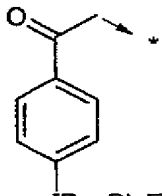

*
F
F
F



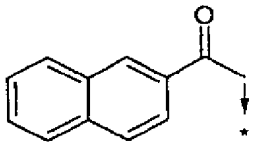
[H, OMe, NO_2, Cl]

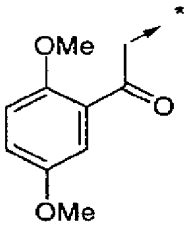


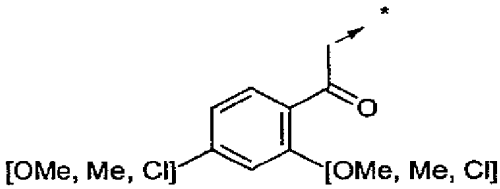
[OMe, NO_2, Br, F, Cl, CN]



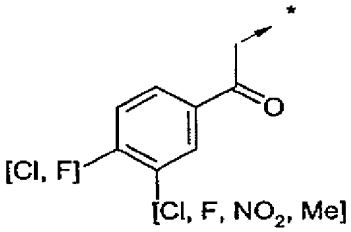
[Br, Cl, F, OMe, Ph, Me, NO_2, N_3, OCF_3, CN, CF_3, NEt_2, nC_4H_9, nC_5H_{11}, OCH_2Ph]



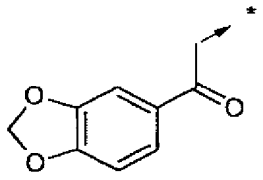


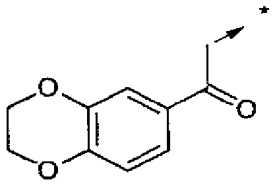


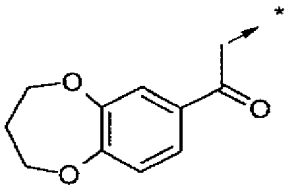
[OMe, Me, Cl] [OMe, Me, Cl]



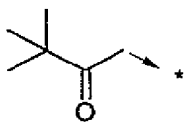
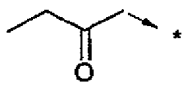
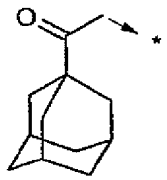
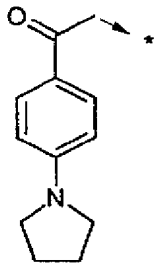
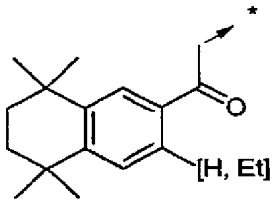
[Cl, F] [Cl, F, NO_2, Me]

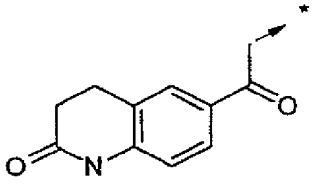
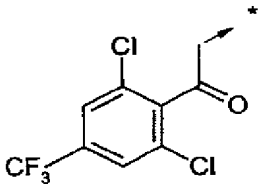


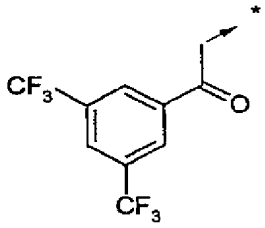


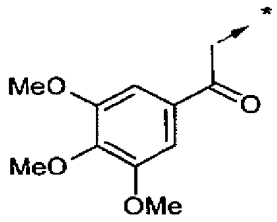


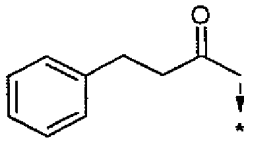
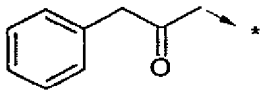
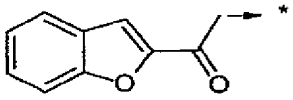
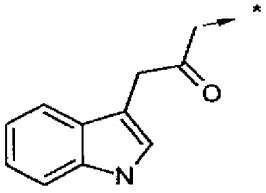
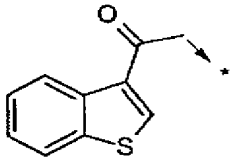
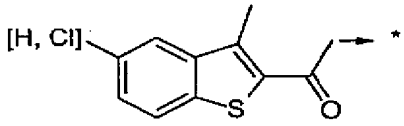
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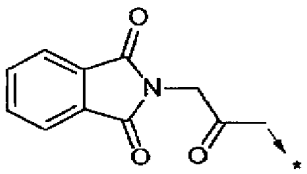
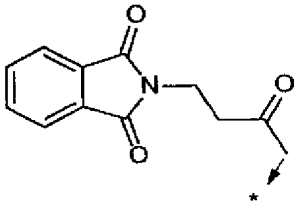
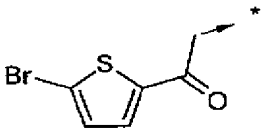










L'invention a également pour objet les procédés de préparation des composés I selon l'invention, en phase solide ou liquide, tels que décrits précédemment.

Les composés I de la présente invention possèdent d'intéressantes propriétés pharmacologiques. C'est ainsi que l'on a découvert que les composés I de la présente invention ont une haute affinité pour un (ou plusieurs) des récepteurs de la somatostatine. Ils peuvent être utilisés comme agonistes ou antagonistes non-peptidiques de la somatostatine de manière sélective ou non.

Les composés de la présente invention peuvent ainsi être utilisés dans différentes applications thérapeutiques. Ils peuvent avantageusement être utilisés pour traiter les états pathologiques ou les maladies tels que présentés ci-dessus et dans lesquels un (ou plusieurs) des récepteurs de la somatostatine est(sont) impliqué(s).

On trouvera ci-après, dans la partie expérimentale, une illustration des propriétés pharmacologiques des composés de l'invention.

La présente demande a également pour objet, à titre de médicaments, les produits de formule I telle que définie ci-dessus, ainsi que les sels d'addition avec les acides minéraux ou organiques pharmaceutiquement acceptables desdits produits de formule I, ainsi que les compositions pharmaceutiques contenant, à titre de principe actif, un au moins des médicaments tels que définis ci-dessus, en association avec un support pharmaceutiquement acceptable.

La composition pharmaceutique peut être sous forme d'un solide, par exemple, des poudres, des granules, des comprimés, des gélules ou des suppositoires. Les supports solides appropriés peuvent être, par exemple, le phosphate de calcium, le stéarate de magnésium, le talc, les sucres, le lactose, la dextrine, l'amidon, la gélatine, la cellulose, la cellulose de méthyle, la cellulose carboxyméthyle de sodium, la polyvinylpyrrolidine et la cire.

Les compositions pharmaceutiques contenant un composé de l'invention peuvent aussi se présenter sous forme liquide, par exemple, des solutions, des émulsions, des suspensions ou des sirops. Les supports liquides appropriés peuvent être, par exemple, l'eau, les solvants organiques tels que le glycérol ou les glycols, de même que leurs mélanges, dans des proportions variées, dans l'eau, additionnés à des huiles ou des graisses pharmaceutiquement acceptables. Les compositions liquides stériles peuvent être utilisées pour les injections intramusculaires, intrapéritonéales ou

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sous-cutanées et les compositions stériles peuvent également être administrée par intraveineuse.

Tous les termes techniques et scientifiques utilisés dans le présent texte ont la signification connue de l'homme de l'art. Par ailleurs, tous les brevets (ou demandes de brevet) ainsi que les autres références bibliographiques sont incorporés par référence.

Partie expérimentale :

D'autres composés selon l'invention obtenus selon les procédures des exemples A, B, C et D précédemment décrites, sont rassemblés dans le tableau ci-dessous.

Les composés sont caractérisés par leur temps de rétention (tr), exprimé en minute, et leur pic moléculaire (M+H+) déterminé par la spectroscopie de masse (SM).

Pour la spectroscopie de masse, un spectomètre de masse simple quadripôle (Micromass, modèle Platform) équipé d'une source électrospray est utilisé avec une résolution de 0,8 Da à 50% de vallée. Les conditions pour les exemples 1 à 778 ci-dessous, sont les suivantes :

Conditions C1 et C2

Eluant : A : Eau+ 0,02 % acide trifluoracétique ; B : acétonitrile

T (min)	*A %*	*B %*
0	100	0
1	100	0
10	15	85
12	15	85

Condition C1	Condition C2
Débit : 1,1 ml/min	Débit : 1,1 ml/min
Injection : 5 µl	Injection : 20 µl
Temp : 40° C	Temp : 40° C
Longueur d'ondes (% UV) : 210 nm	Longueur d'ondes (% UV) : 210 nm
Colonne : Uptisphere ODS 3 µm	Colonne : Kromasyl ODS 3,5 µm
33 * 4,6 mm i.d	50 * 4,6 mm i.d

Conditions C3

Eluant : A : Eau+ 0,02 % acide trifluoracétique ; B : acétonitrile

T (min)	*A %*	*B %*
0	90	10
6	15	85
10	15	85

Debit : 1 ml/min

Injection : 5 µl

Colonne : Uptisphere ODS 3 µm 50 * 4,6 mm i.d

Temp : 40° C

Longueur d'ondes (% UV) : 220 nm

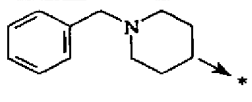
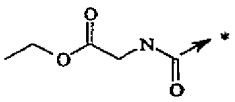
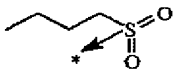
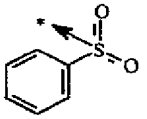
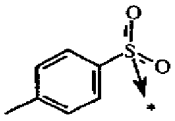
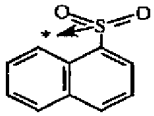
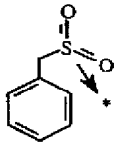
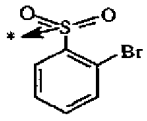
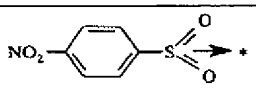
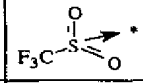
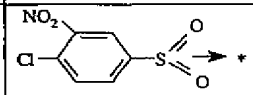
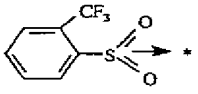
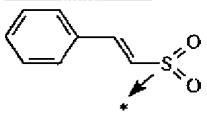
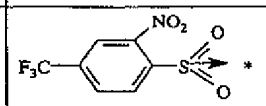
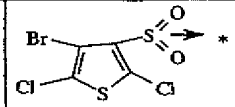
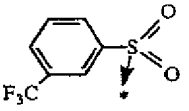
Les conditions suivant les exemples, sont les suivantes :

Exemples	Conditions
1 à 29	C2
30 à 263	C1
264 à 425	C3
426 à 456	C2
457 à 503	C3
504 à 586	C1
587 à 778	C3

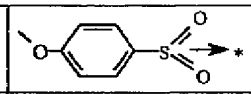
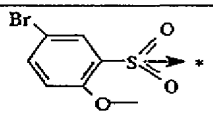
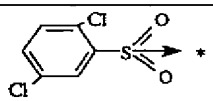
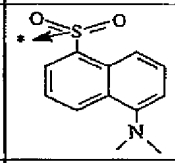
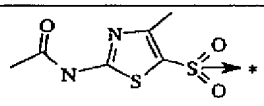
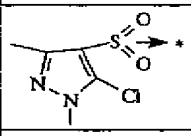
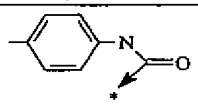
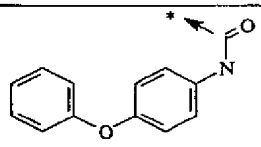
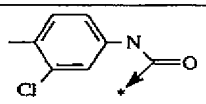
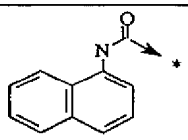
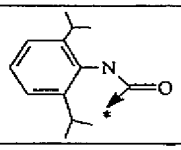
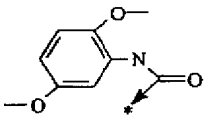
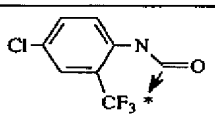
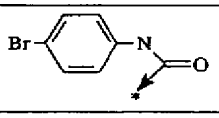
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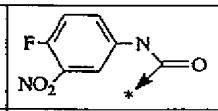
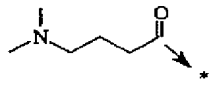
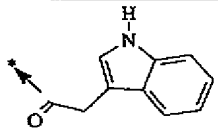
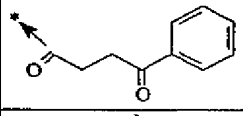
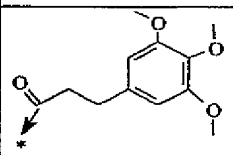
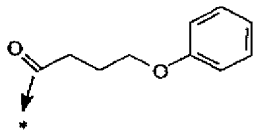
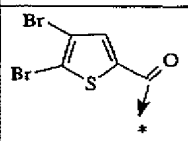
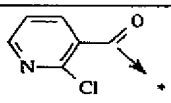
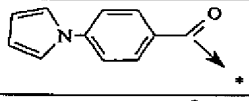
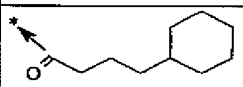
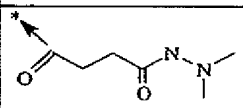
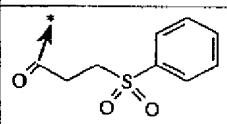
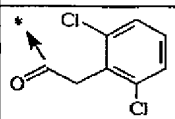
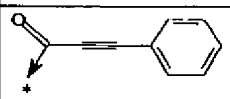
Ces exemples sont présentés pour illustrer les procédures ci-dessus et ne doivent en aucun cas être considérés comme une limite à la portée de l'invention.

Le symbole -> * correspond au point de rattachement du radical.

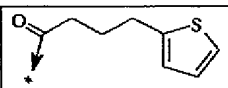
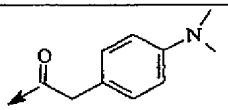
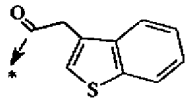
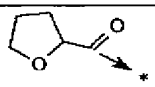
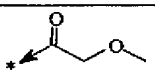
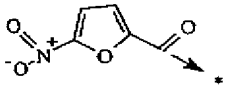
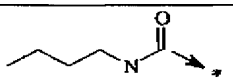
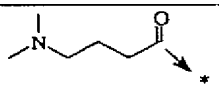
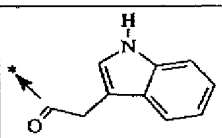
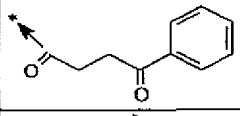
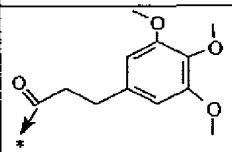
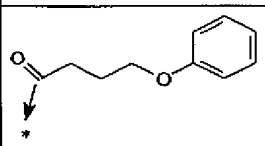
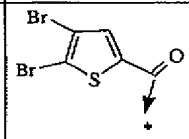
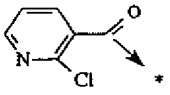
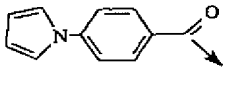
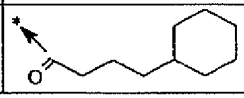
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2	"	"		94	7,7	543,2
3	"	"		96	8,1	557,2
4	"	"		98	8,5	593,2
5	"	"		95	7,8	557,2
6	"	"		97	8,1	623,1
7	"	"		95	8,1	588,2
8	"	"		19	8,1	535,2
9	"	"		99	8,5	622,2
10	"	"		80	8,4	611,2
11	"	"		99	8,2	569,2
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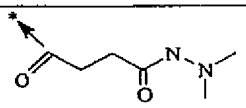
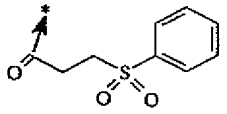
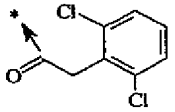
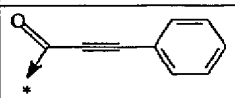
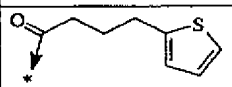
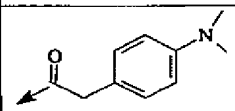
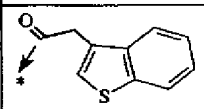
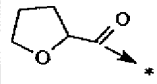
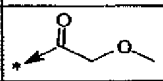
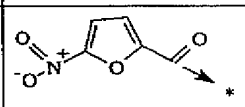
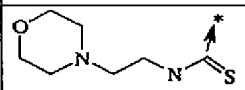
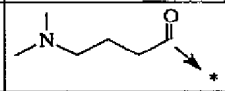
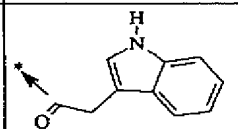
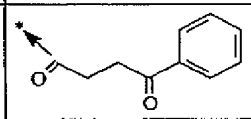
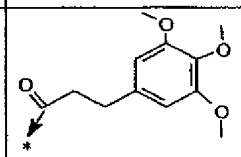
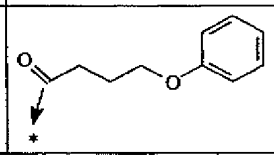
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19	"	"		83	7,2	621,2
20	"	"		98	7,4	595,2
21	"	"		84	7,4	536,3
22	"	"		99	8,4	614,3
23	"	"		63	8,2	570,2
24	"	"		92	7,5	572,3
25	"	"		93	8,4	606,4
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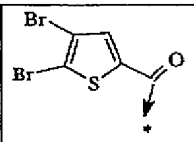
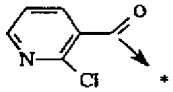
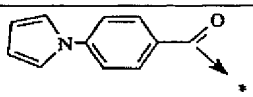
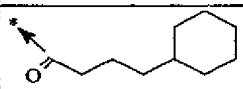
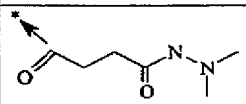
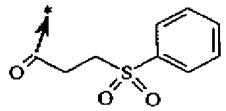
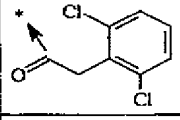
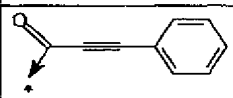
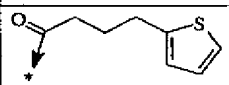
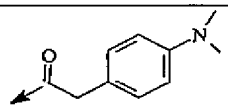
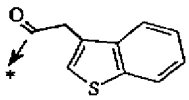
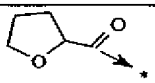
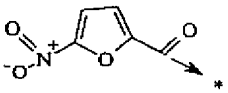
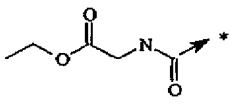
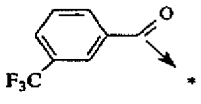
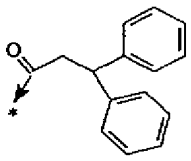
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34	"	"		85,41	6,0	565,4
35	"	"		98,4	6,4	671,1
36	"	"		86	4,9	542,3
37	"	"		89	6,1	572,3
38	"	"		77,61	6,8	555,4
39	"	"		89,16	4,2	545,4
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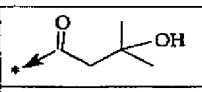
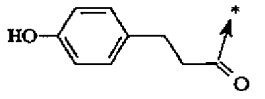
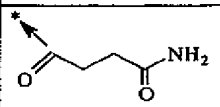
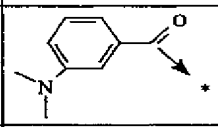
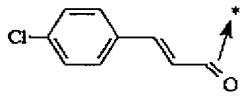
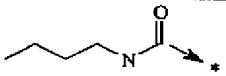
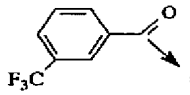
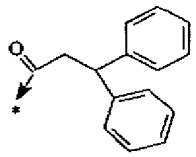
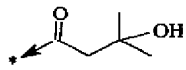
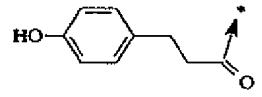
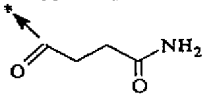
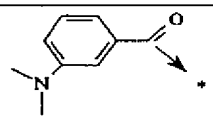
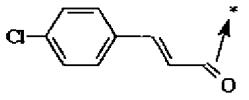
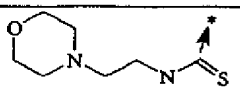
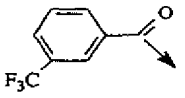
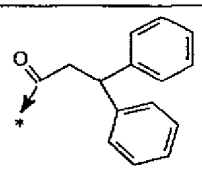
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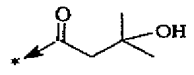
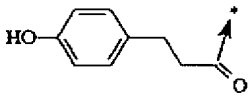
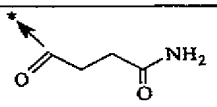
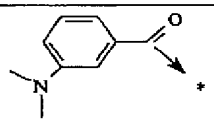
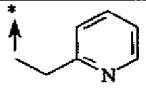
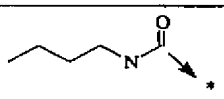
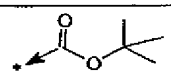
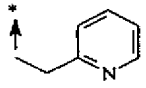
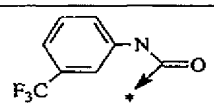
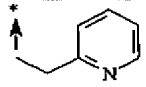
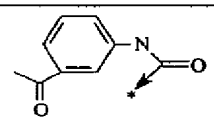
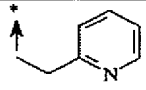
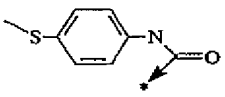
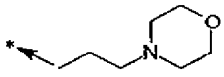
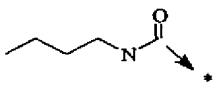
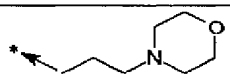
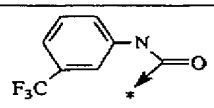
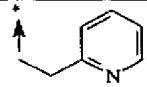
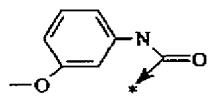
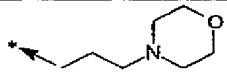
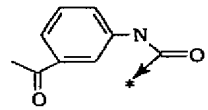
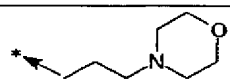
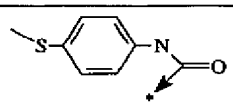
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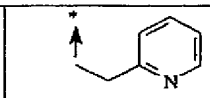
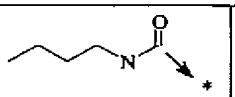
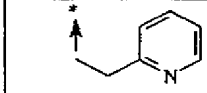
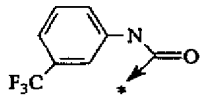
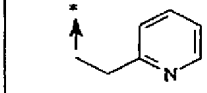
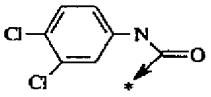
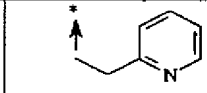
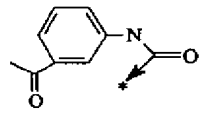
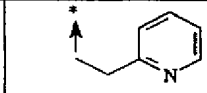
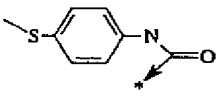
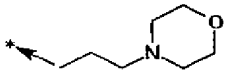
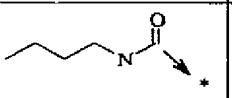
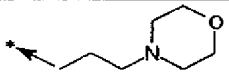
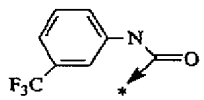
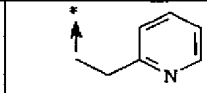
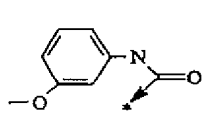
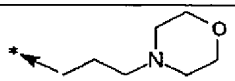
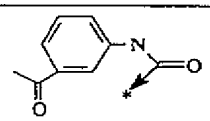
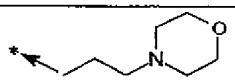
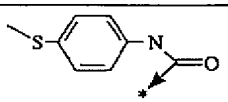
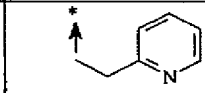
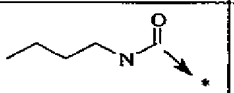
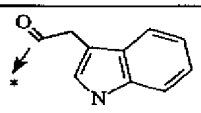
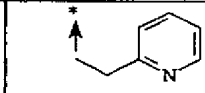
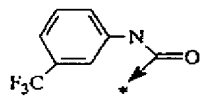
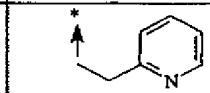
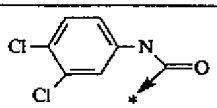
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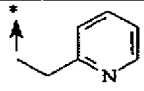
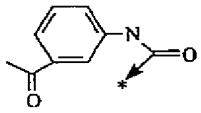
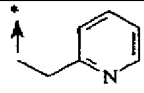
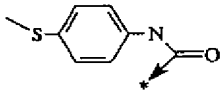
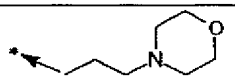
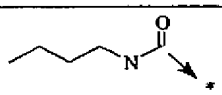
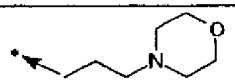
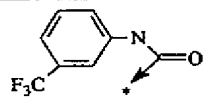
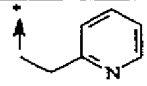
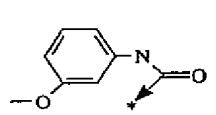
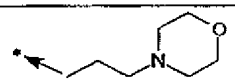
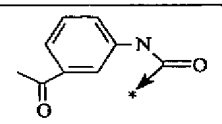
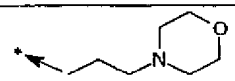
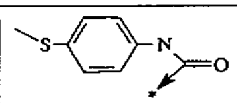
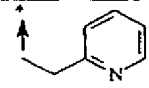
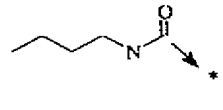
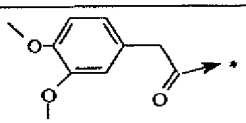
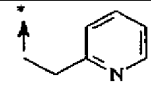
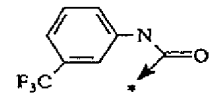
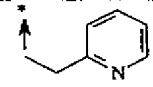
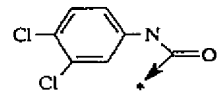
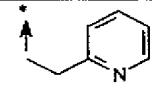
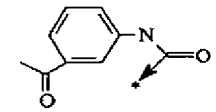
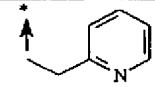
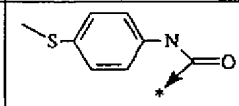
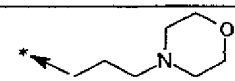
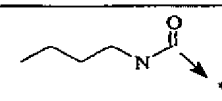
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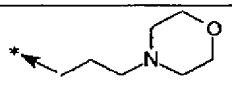
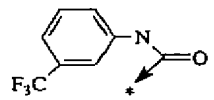
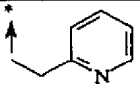
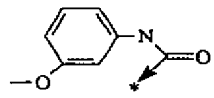
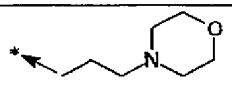
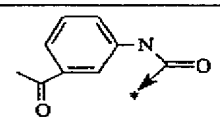
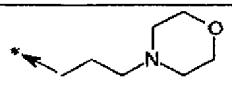
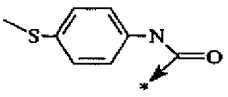
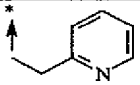
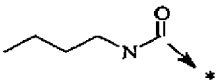
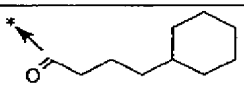
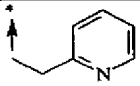
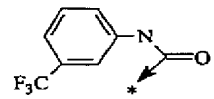
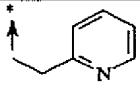
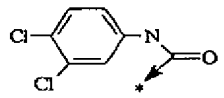
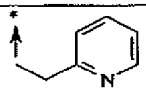
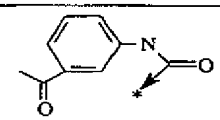
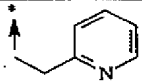
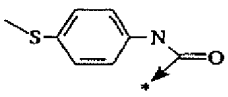
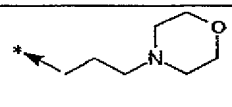
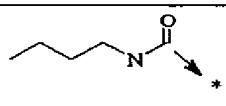
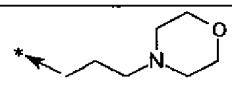
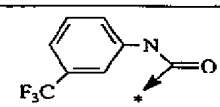
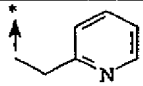
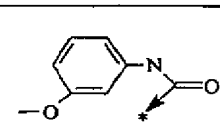
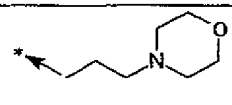
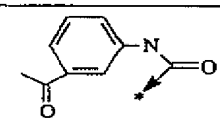
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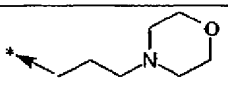
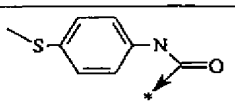
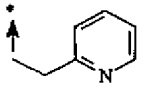
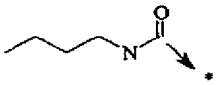
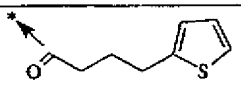
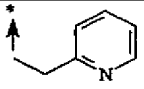
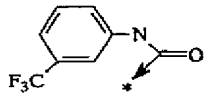
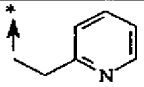
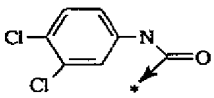
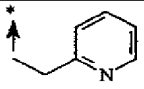
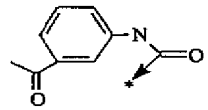
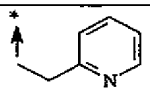
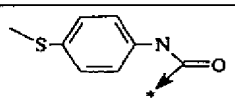
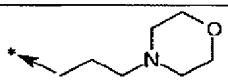
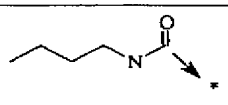
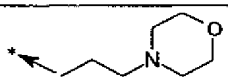
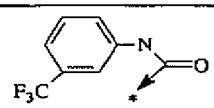
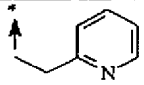
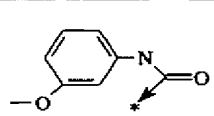
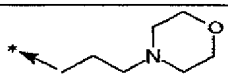
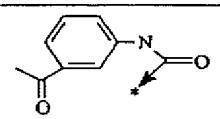
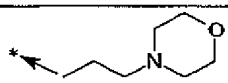
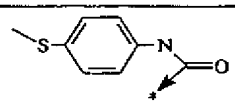
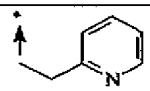
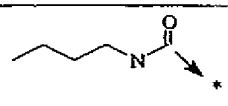
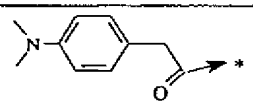
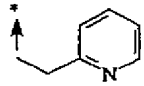
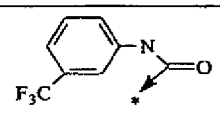
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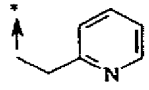
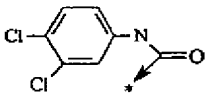
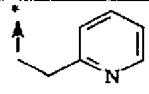
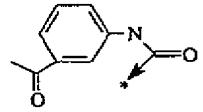
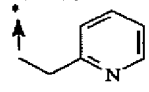
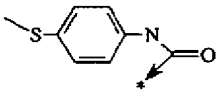
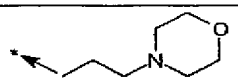
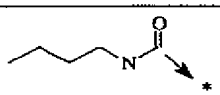
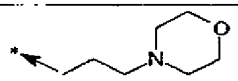
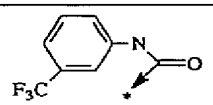
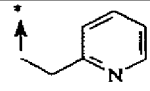
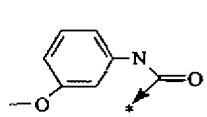
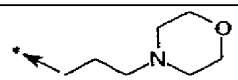
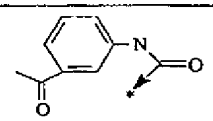
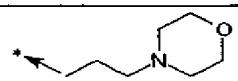
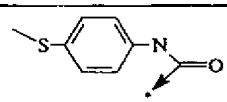
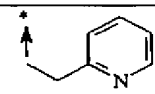
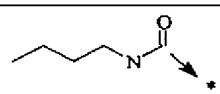
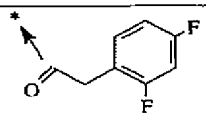
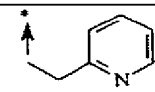
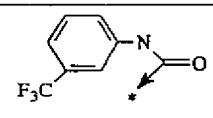
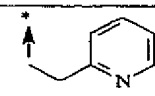
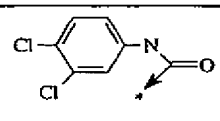
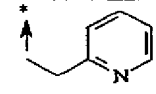
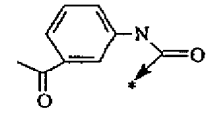
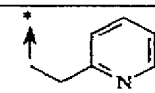
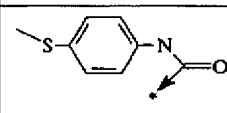
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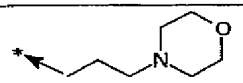
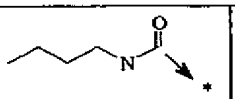
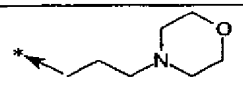
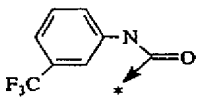
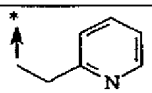
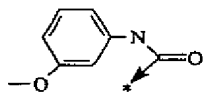
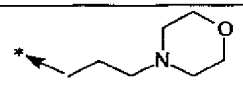
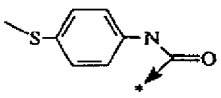
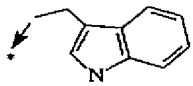
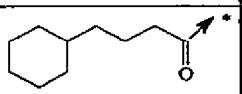
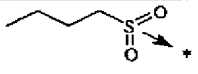
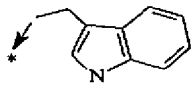
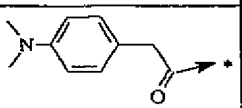
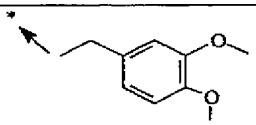
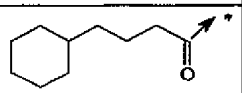
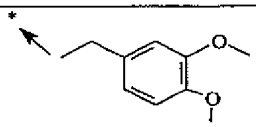
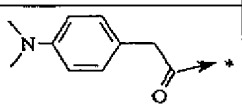
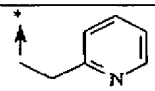
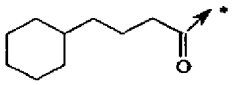
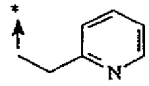
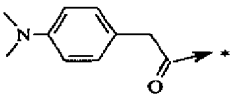
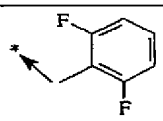
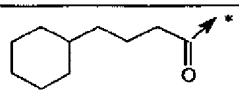
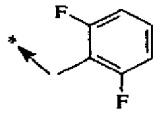
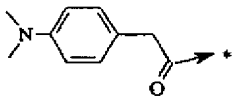
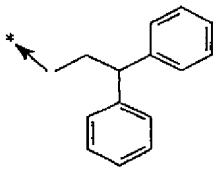
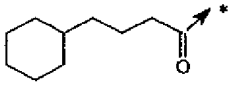
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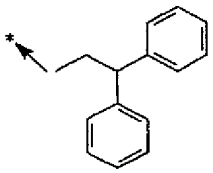
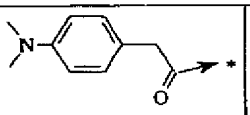
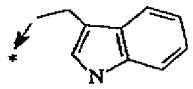
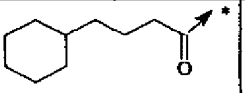
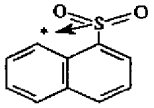
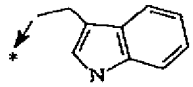
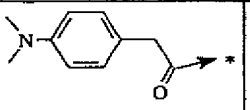
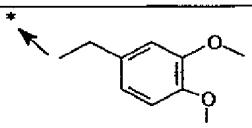
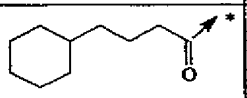
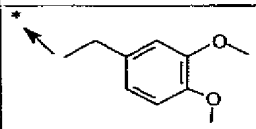
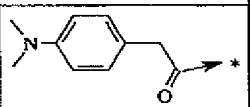
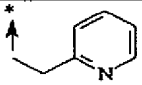
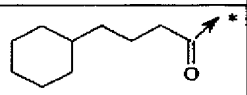
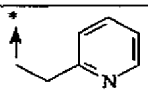
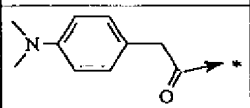
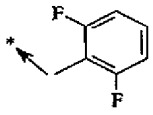
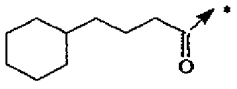
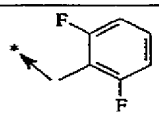
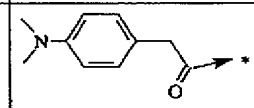
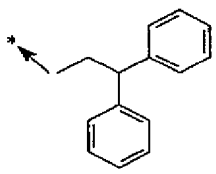
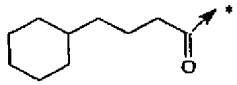
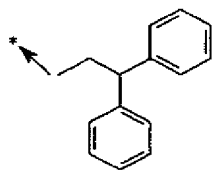
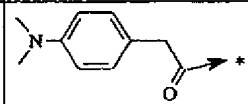
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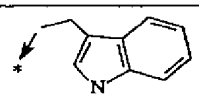
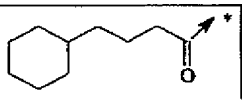
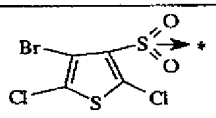
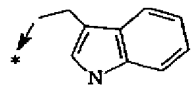
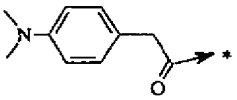
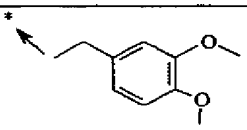
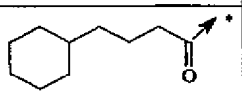
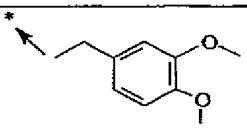
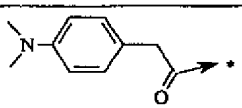
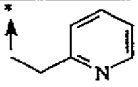
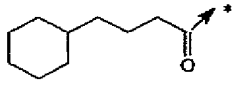
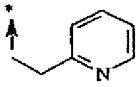
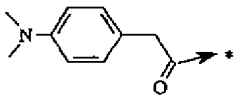
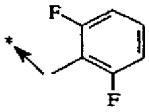
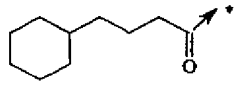
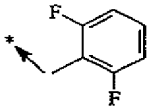
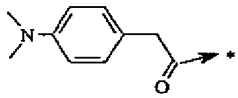
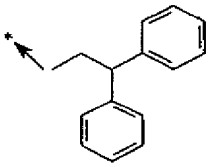
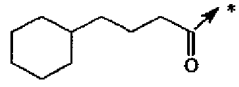
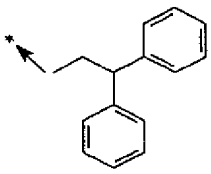
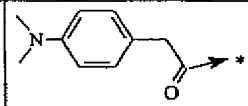
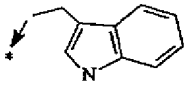
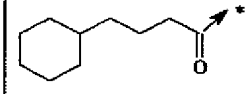
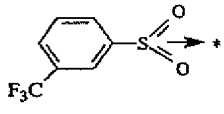
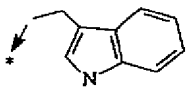
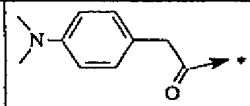
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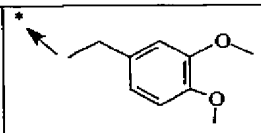
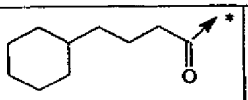
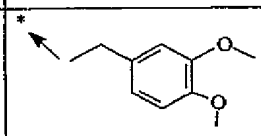
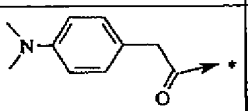
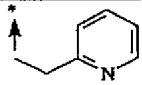
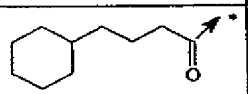
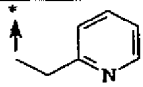
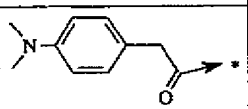
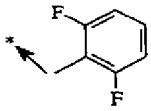
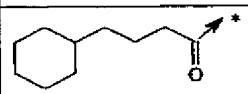
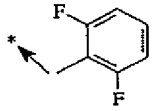
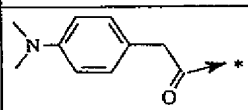
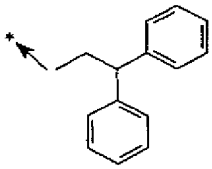
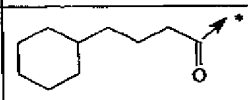
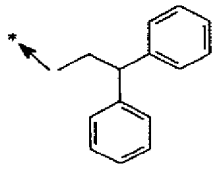
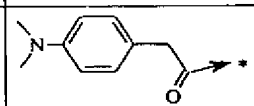
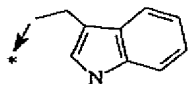
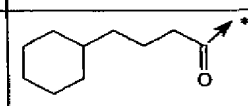
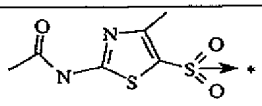
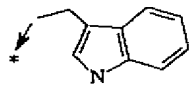
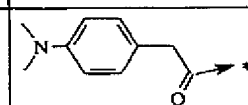
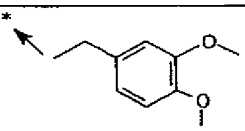
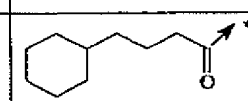
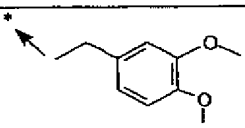
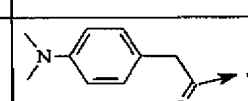
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199			"	94	5,6	557,3
200			"	98	10,8	569,2
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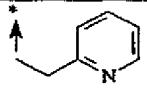
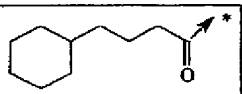
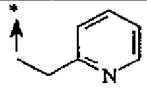
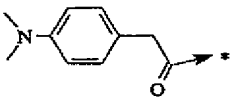
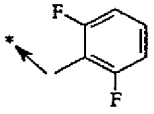
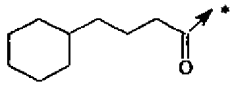
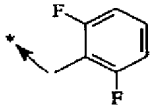
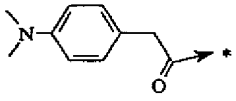
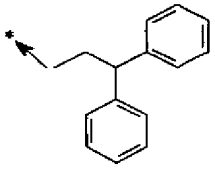
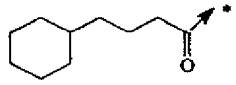
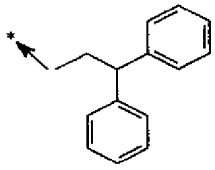
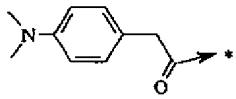
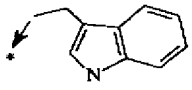
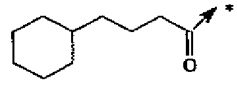
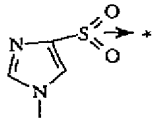
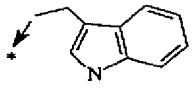
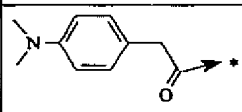
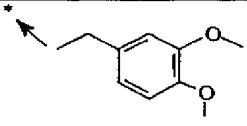
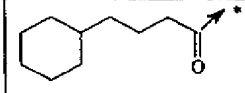
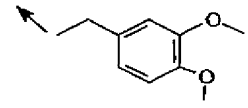
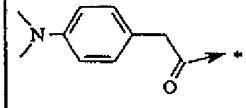
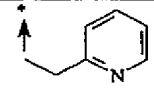
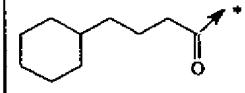
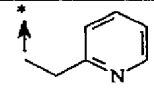
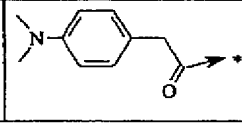
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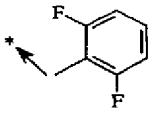
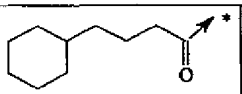
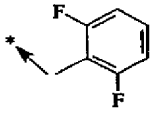
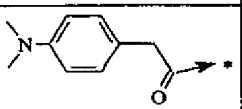
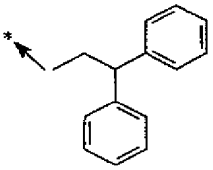
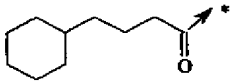
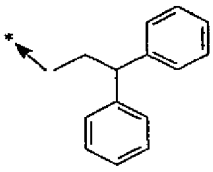
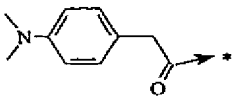
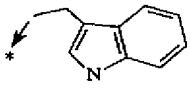
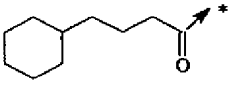
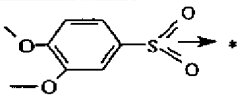
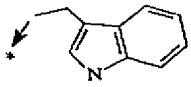
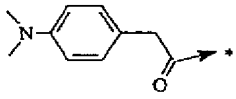
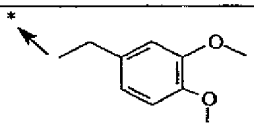
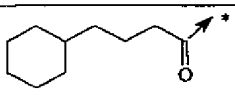
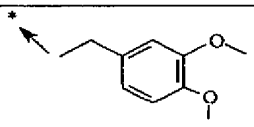
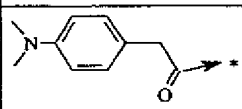
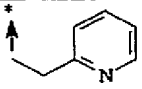
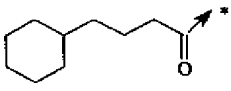
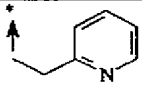
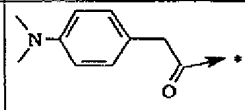
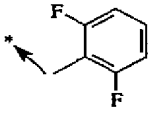
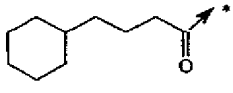
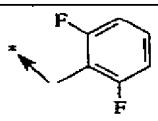
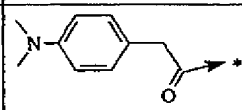
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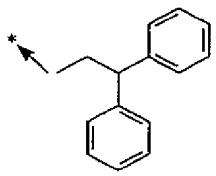
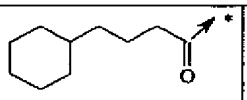
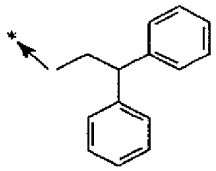
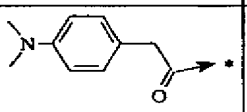
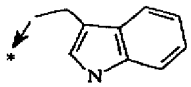
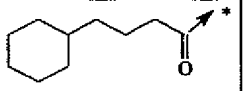
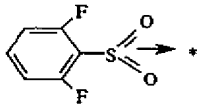
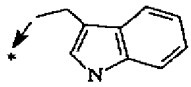
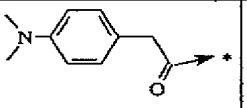
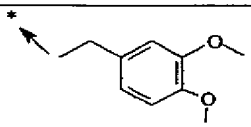
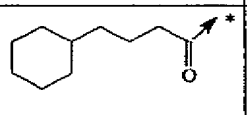
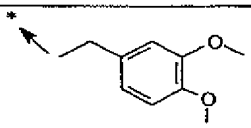
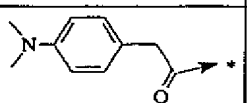
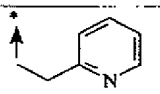
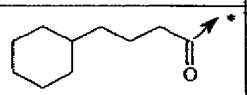
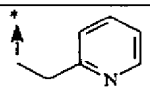
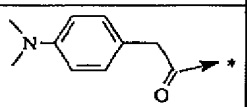
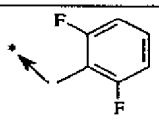
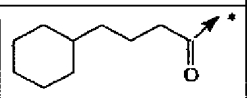
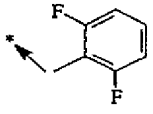
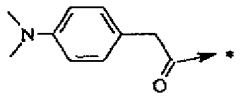
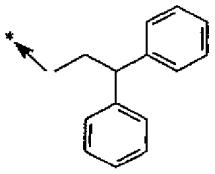
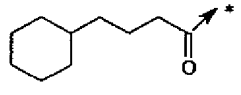
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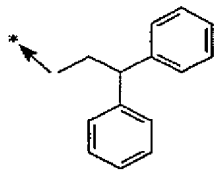
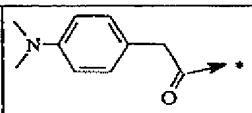
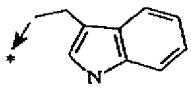
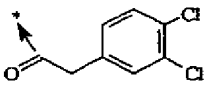
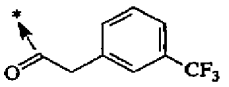
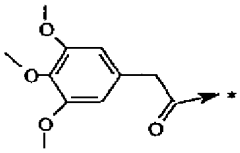
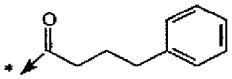
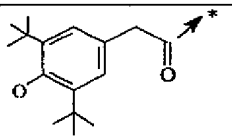
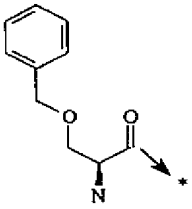
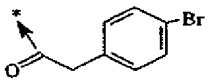
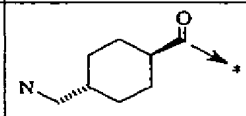
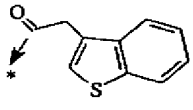
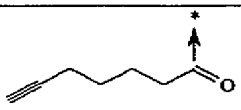
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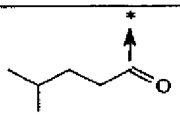
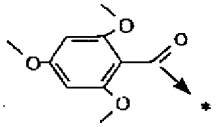
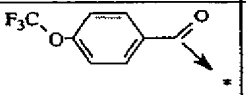
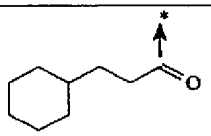
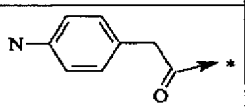
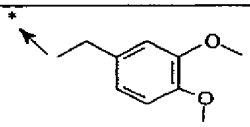
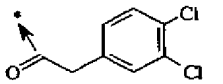
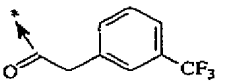
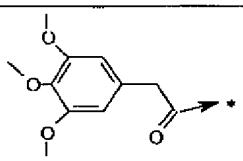
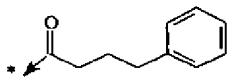
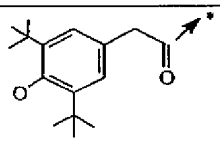
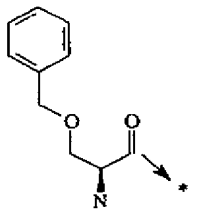
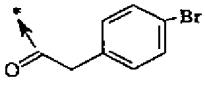
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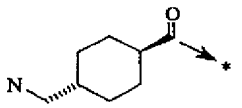
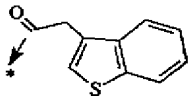
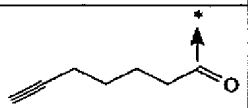
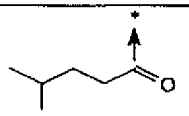
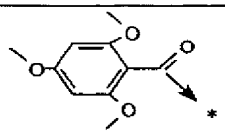
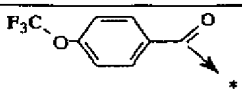
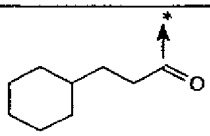
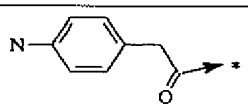
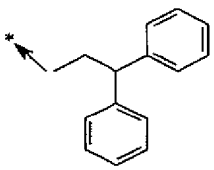
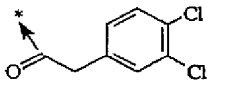
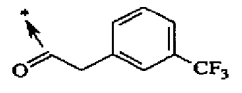
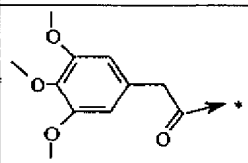
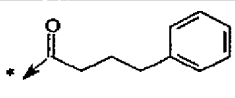
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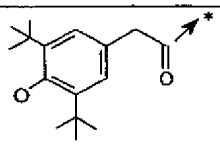
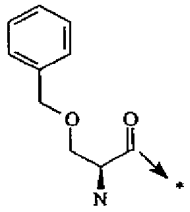
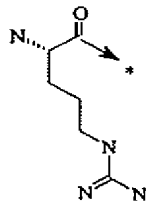
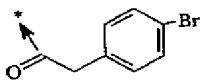
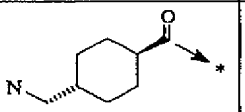
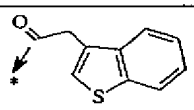
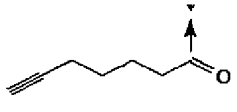
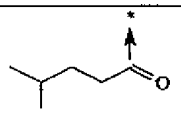
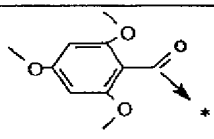
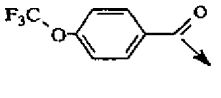
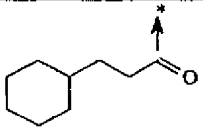
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268	"		"	92,82	5,6	490,4
269	"		"	68,87	3,6	421,3
270	"		"	79,07	4,9	440,2
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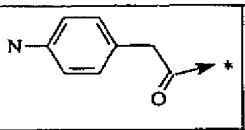
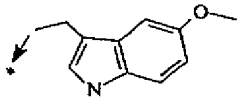
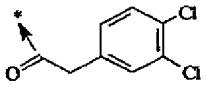
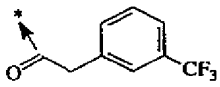
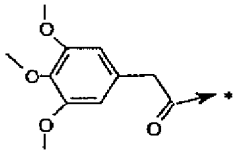
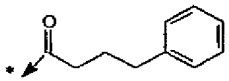
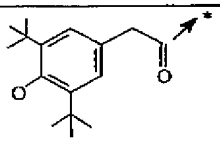
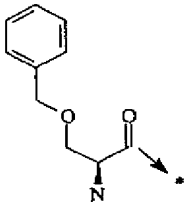
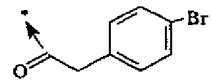
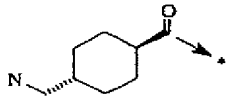
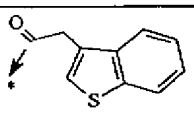
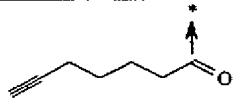
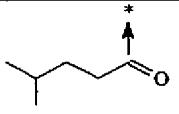
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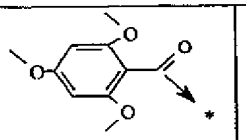
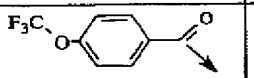
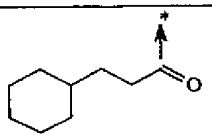
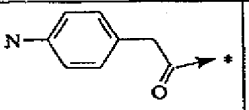
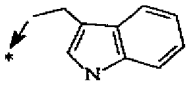
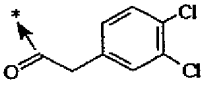
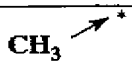
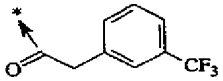
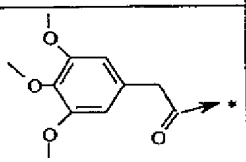
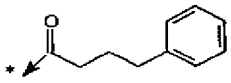
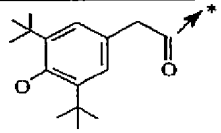
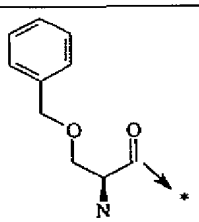
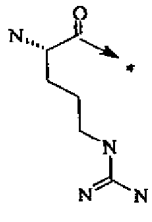
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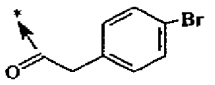
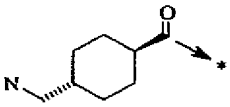
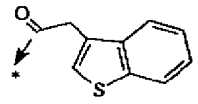
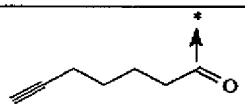
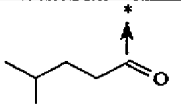
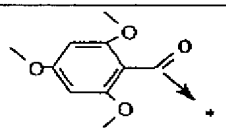
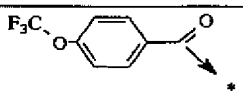
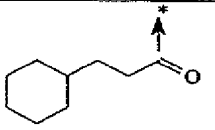
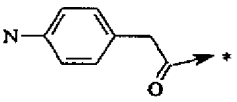
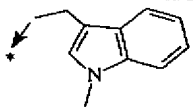
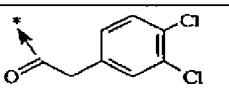
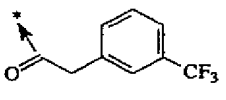
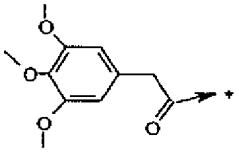
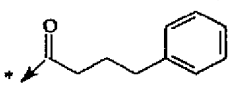
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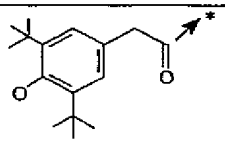
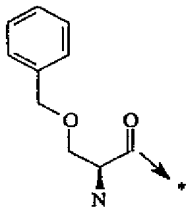
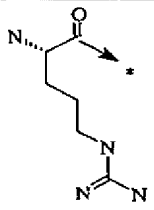
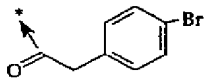
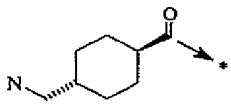
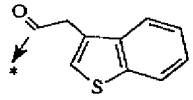
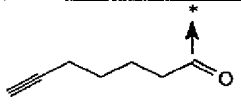
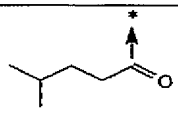
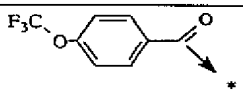
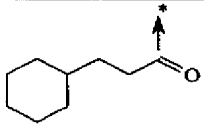
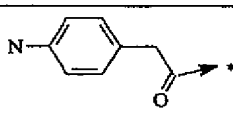
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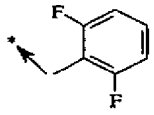
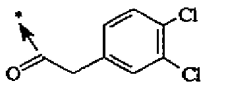
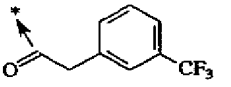
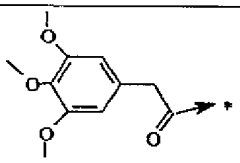
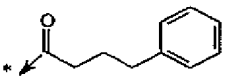
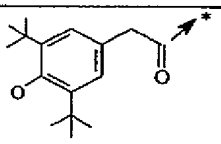
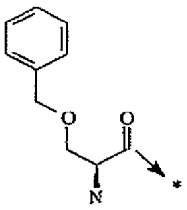
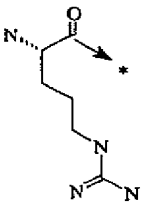
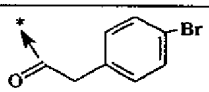
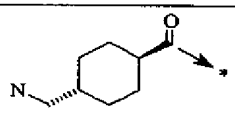
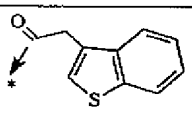
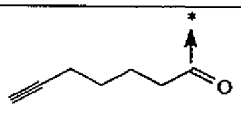
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324	"		"	83,35	3,1	407,3
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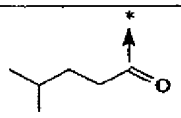
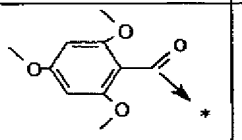
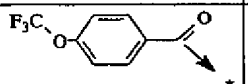
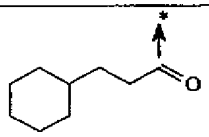
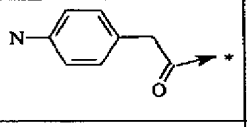
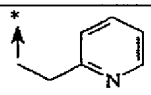
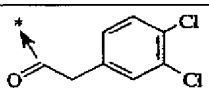
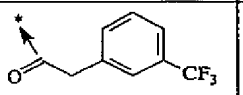
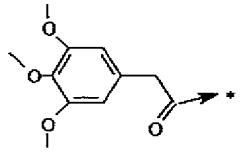
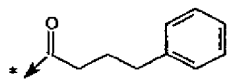
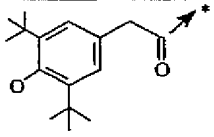
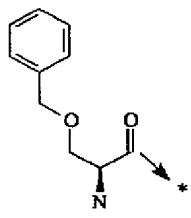
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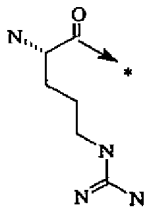
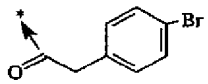
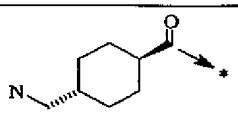
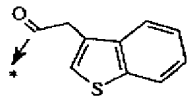
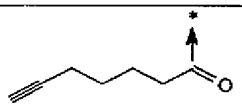
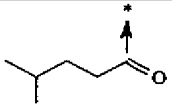
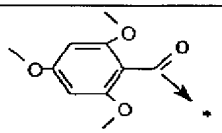
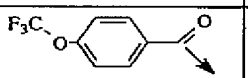
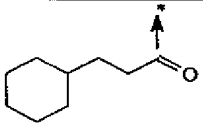
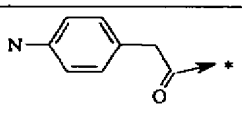
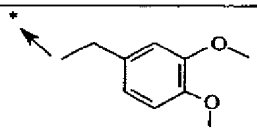
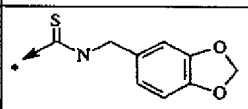
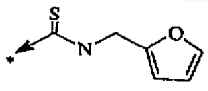
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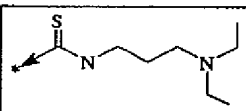
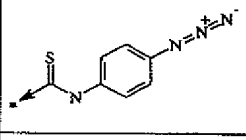
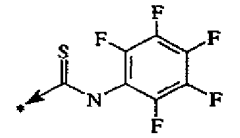
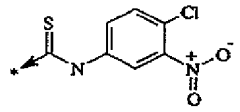
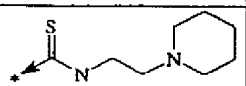
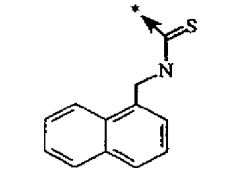
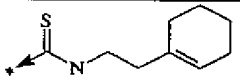
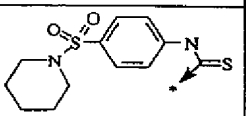
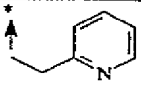
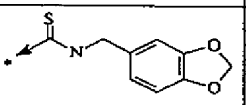
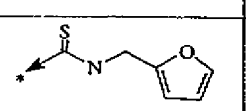
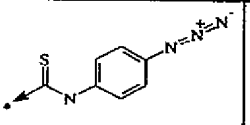
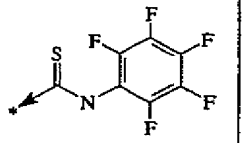
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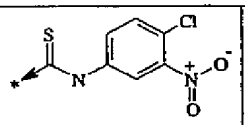
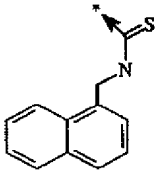
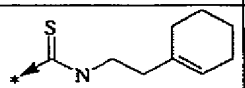
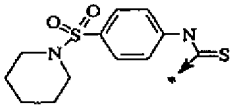
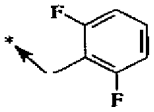
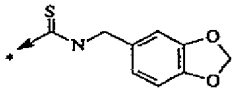
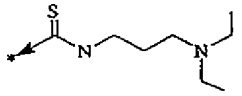
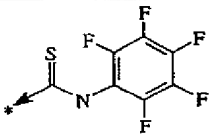
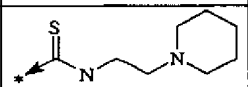
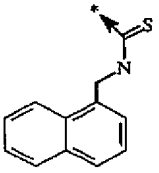
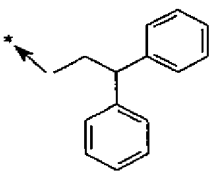
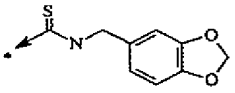
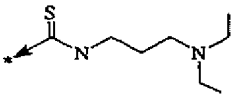
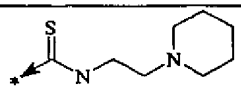
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371	"		"	99,1	2,6	360,2
372			"	90,59	3,4	392,1
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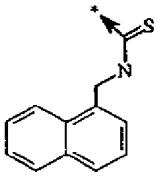
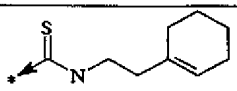
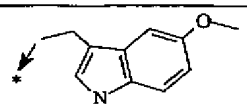
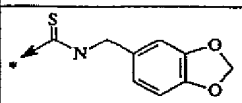
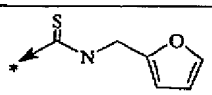
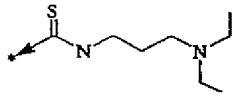
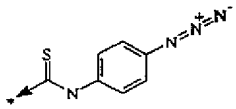
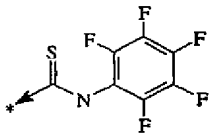
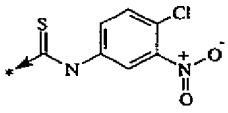
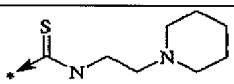
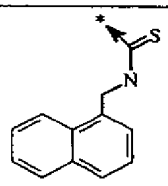
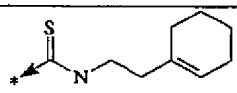
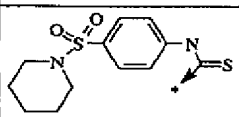
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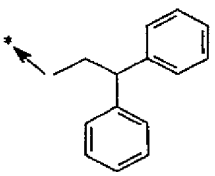
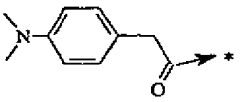
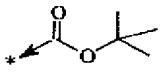
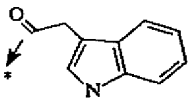
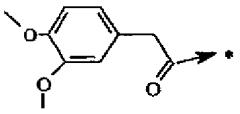
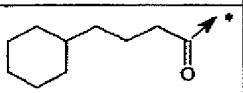
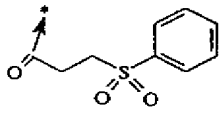
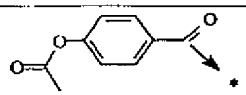
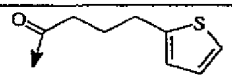
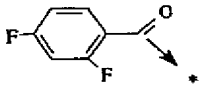
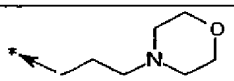
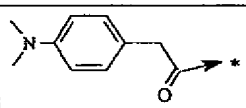
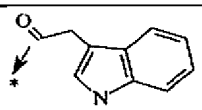
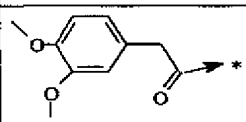
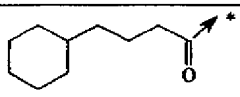
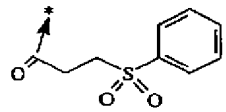
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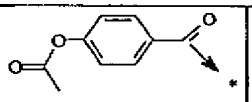
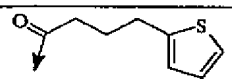
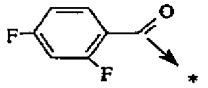
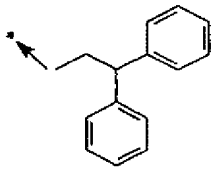
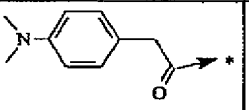
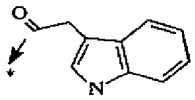
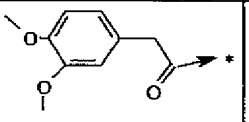
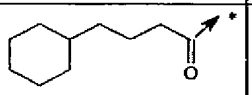
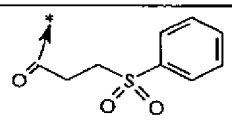
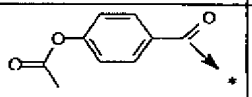
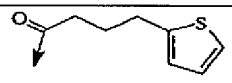
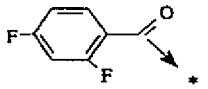
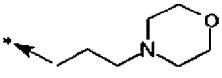
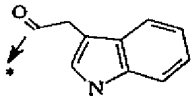
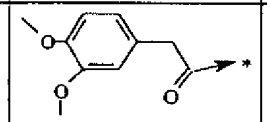
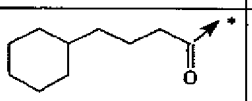
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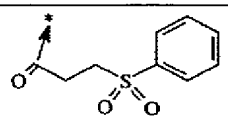
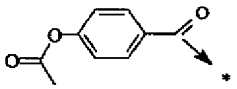
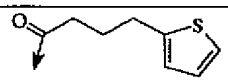
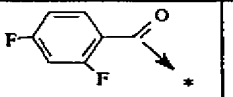
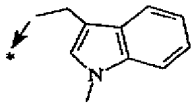
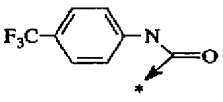
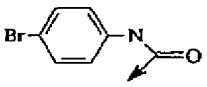
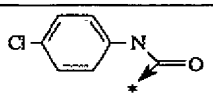
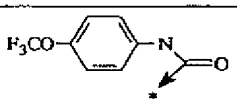
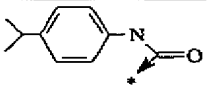
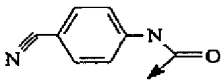
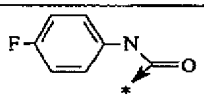
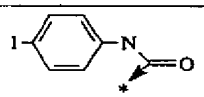
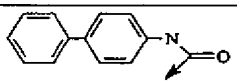
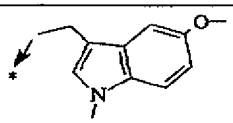
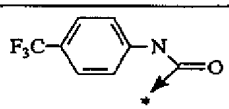
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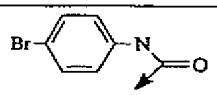
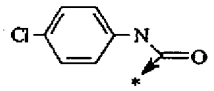
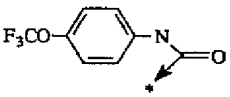
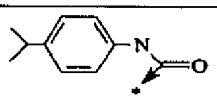
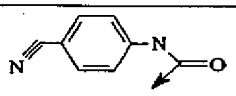
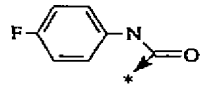
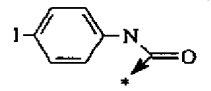
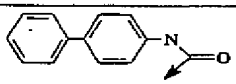
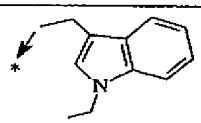
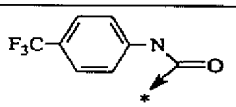
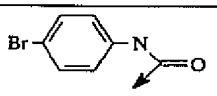
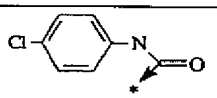
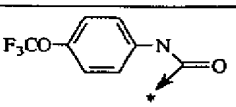
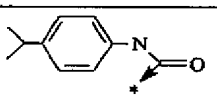
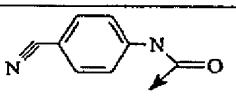
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420	"		"	76,94	4,7	499,2
421	"		"	85,12	4,6	488,2
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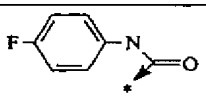
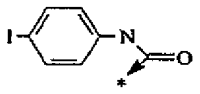
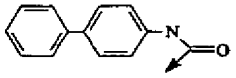
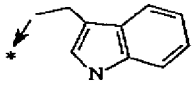
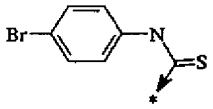
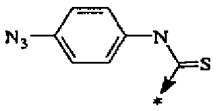
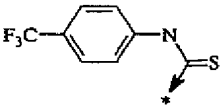
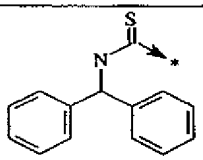
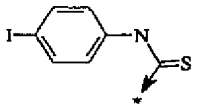
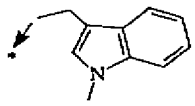
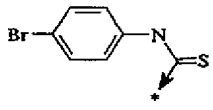
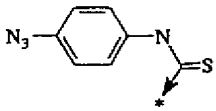
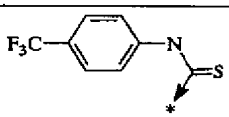
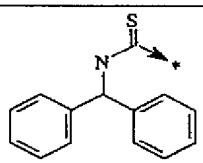
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431	"		"	66,60	9,7	557,3
432	"		"	97,25	10,5	547,3
433	"		"	98,20	10,2	549,3
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435	"		"	94,30	5,8	485,3
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447	"		"	85,40	6,3	457,2
448	"		"	96,70	6,9	447,2
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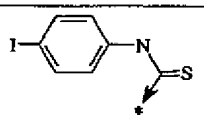
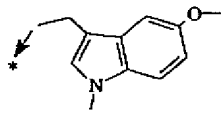
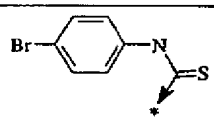
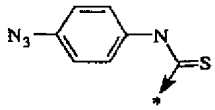
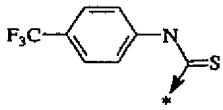
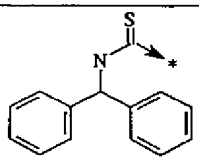
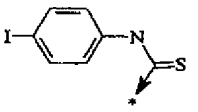
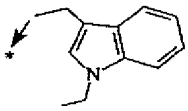
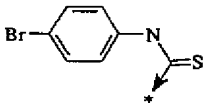
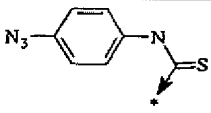
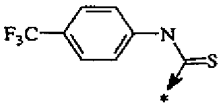
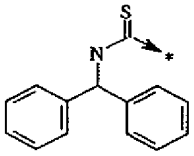
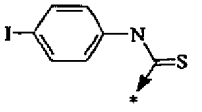
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459	"		"	95,6	4,7	411,3
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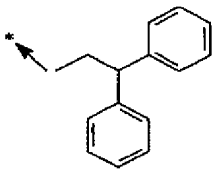
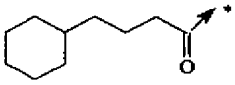
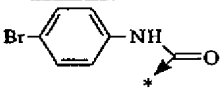
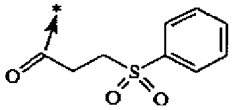
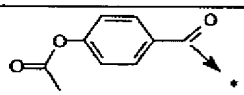
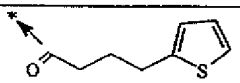
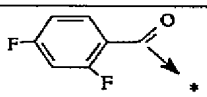
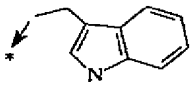
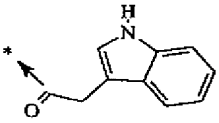
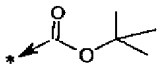
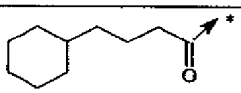
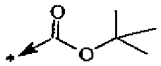
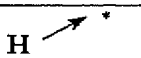
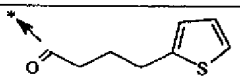
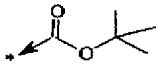
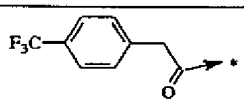
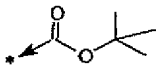
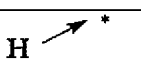
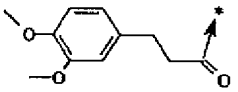
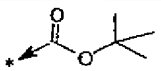
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474	"		"	94,13	5,0	483,4
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480	"		"	93	4,4	416,3

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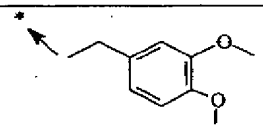
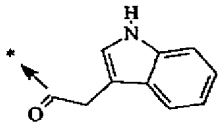
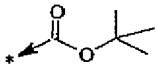
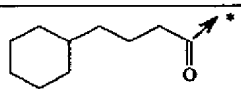
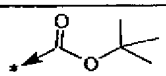
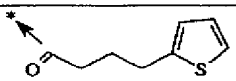
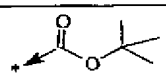
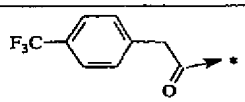
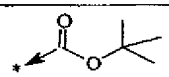
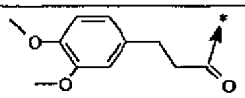
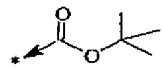
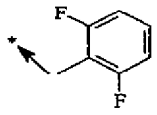
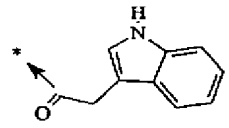
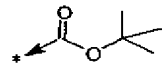
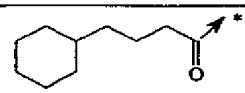
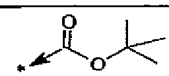
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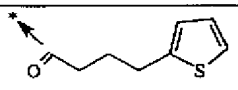
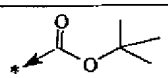
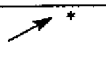
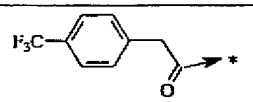
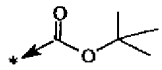
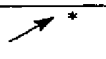
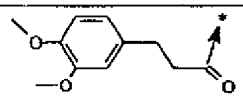
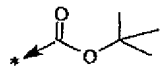
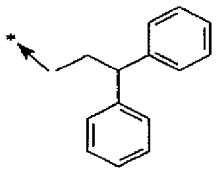
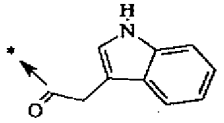
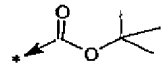
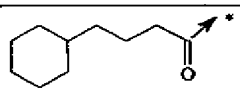
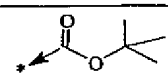
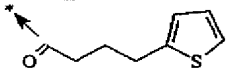
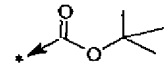
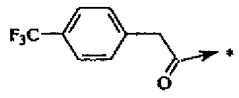
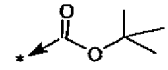
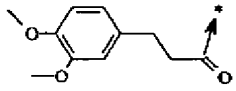
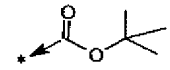
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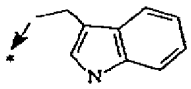
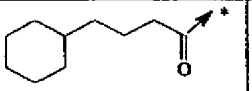
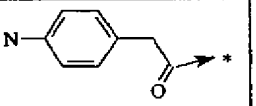
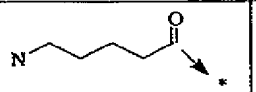
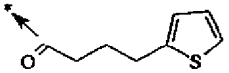
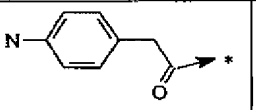
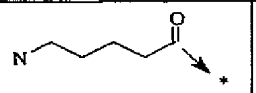
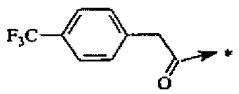
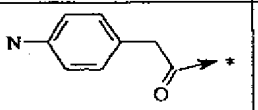
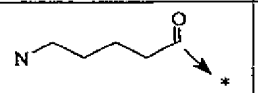
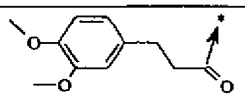
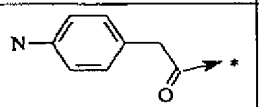
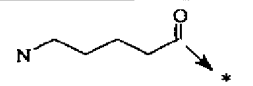
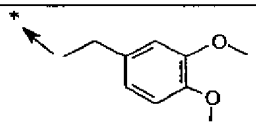
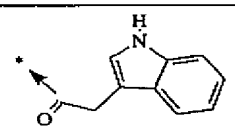
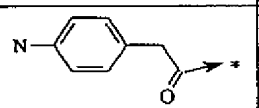
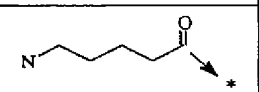
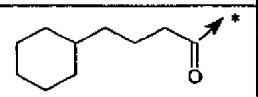
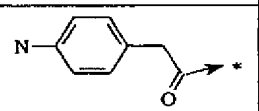
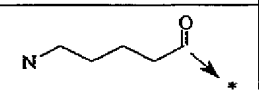
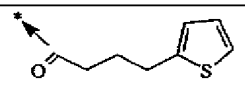
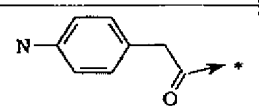
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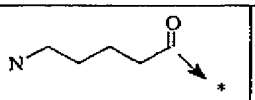
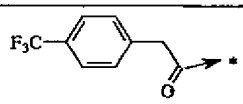
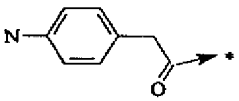
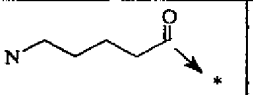
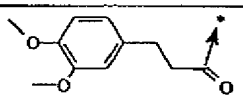
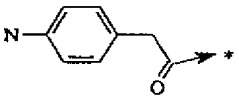
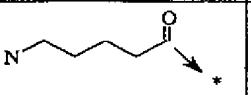
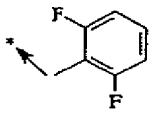
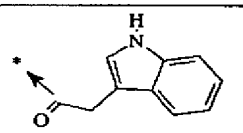
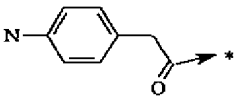
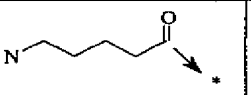
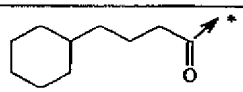
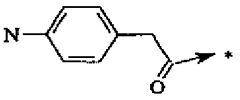
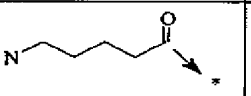
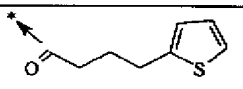
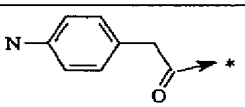
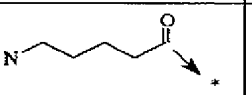
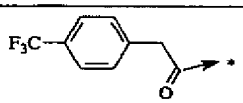
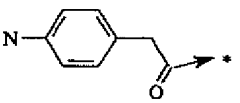
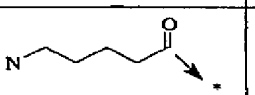
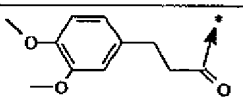
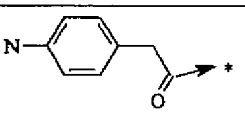
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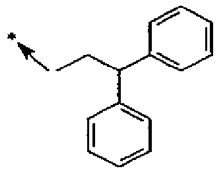
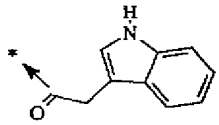
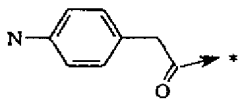
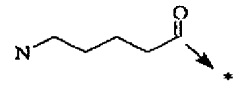
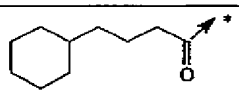
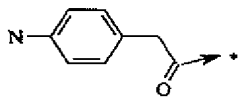
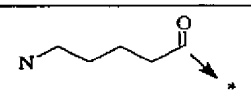
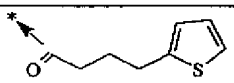
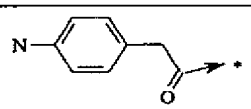
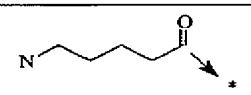
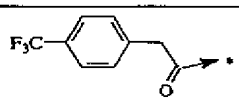
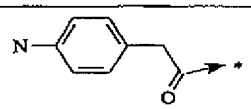
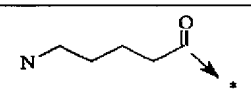
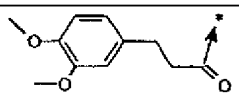
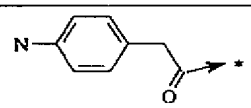
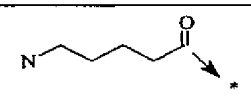
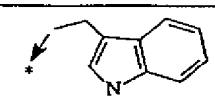
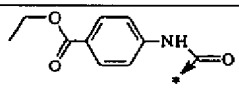
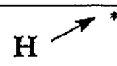
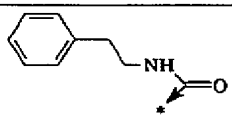
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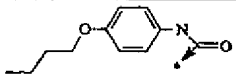
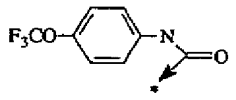
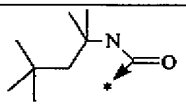
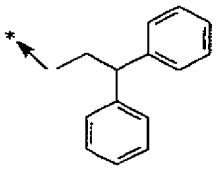
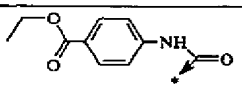
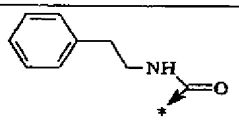
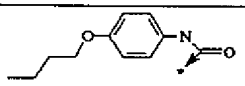
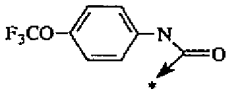
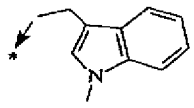
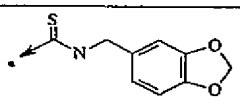
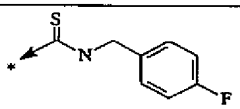
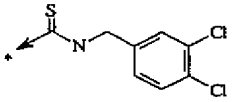
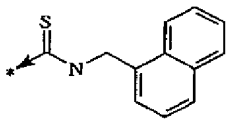
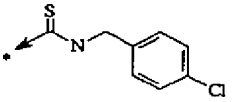
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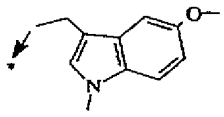
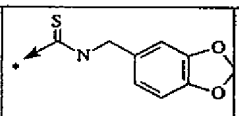
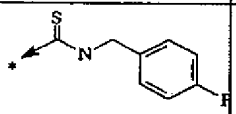
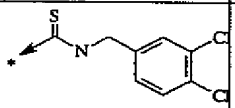
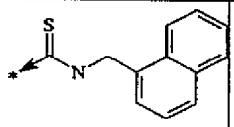
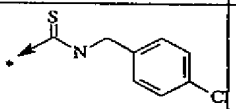
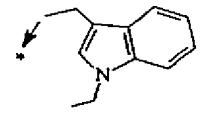
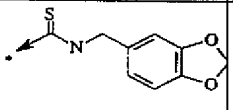
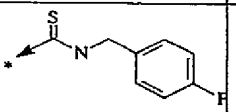
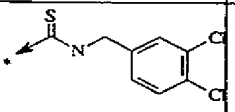
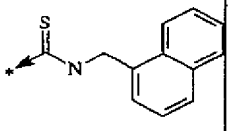
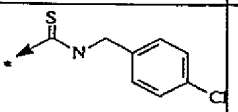
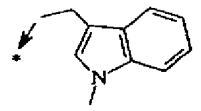
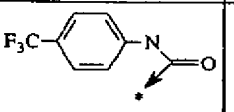
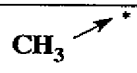
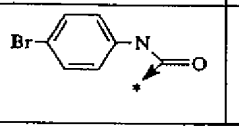
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566	"	"		87,77	5,5	556,3
567				86	6,0	517,3
568	"	"		83,41	5,7	483,3
569	"			95	7,6	512,3
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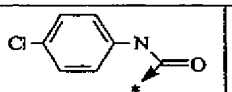
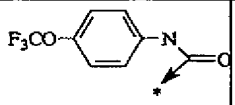
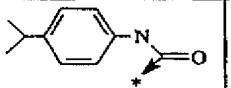
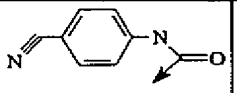
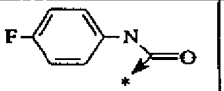
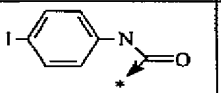
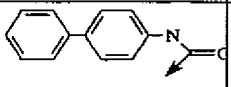
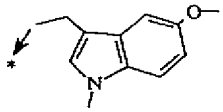
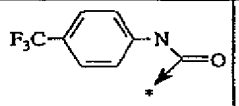
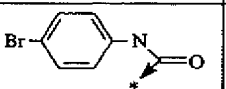
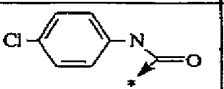
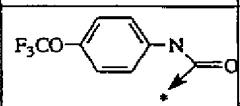
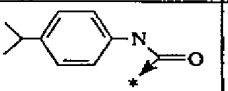
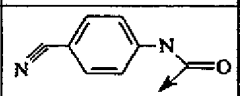
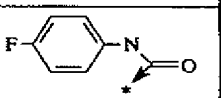
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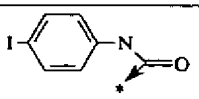
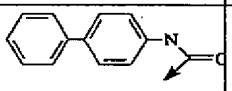
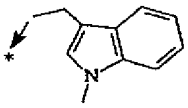
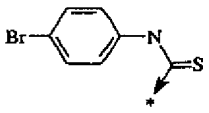
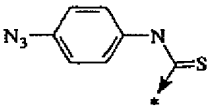
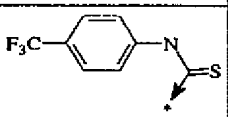
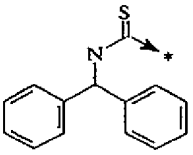
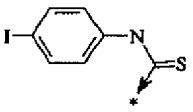
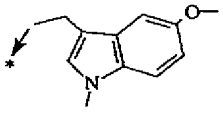
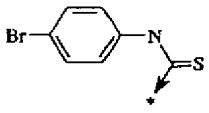
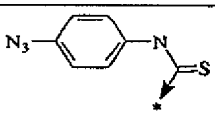
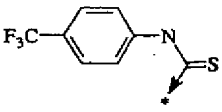
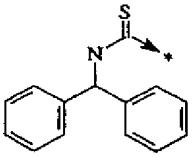
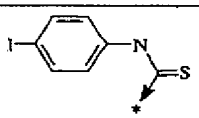
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595	"		"	79	5,5	498,3
596			"	93,4	4,68	451,29
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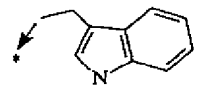
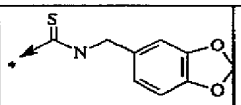
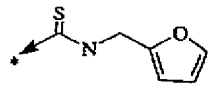
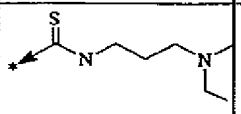
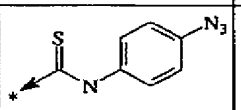
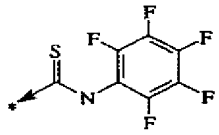
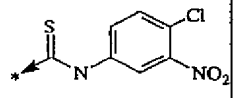
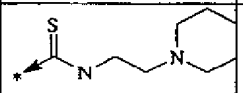
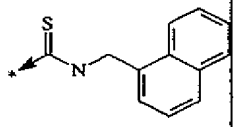
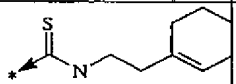
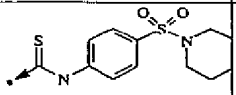
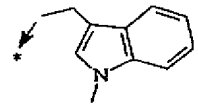
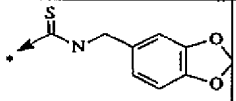
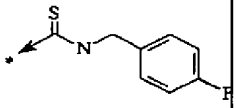
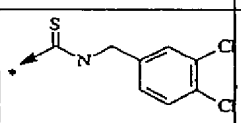
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607	"		"	98,2	5,03	439,29
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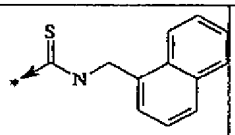
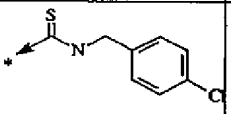
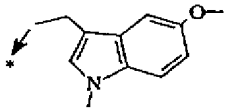
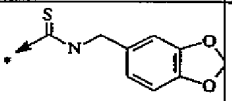
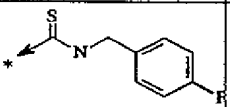
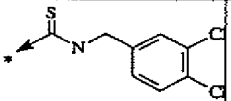
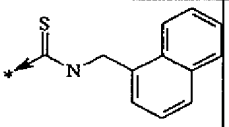
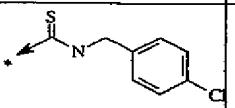
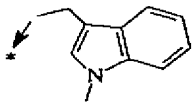
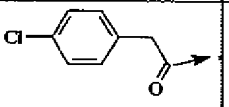
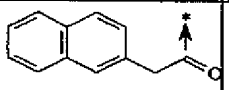
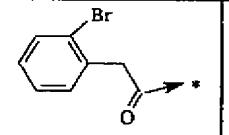
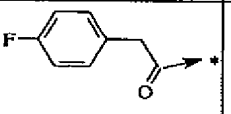
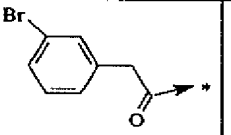
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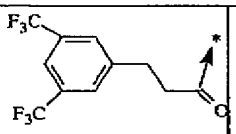
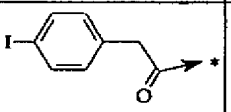
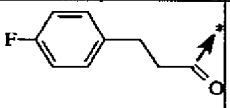
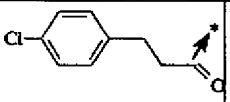
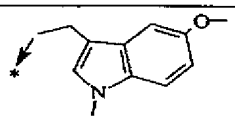
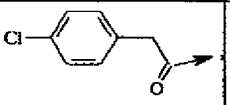
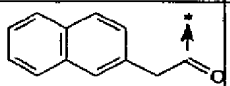
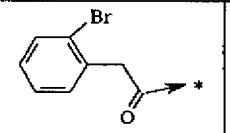
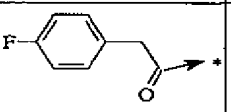
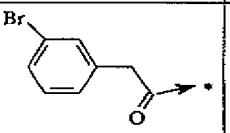
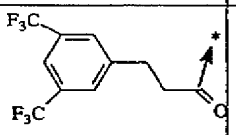
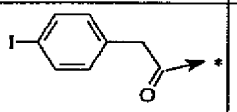
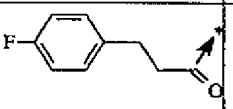
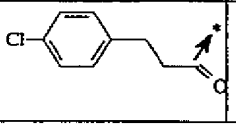
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618	"		"	93,85	5,0	517,2
619	"		"	92,74	5,1	467,4
620			"	91	4,8	489,3
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622	"		"	89,71	4,6	455,3
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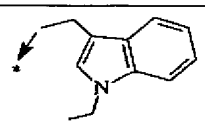
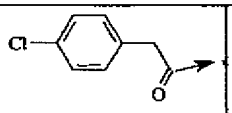
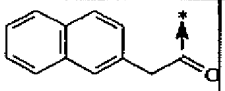
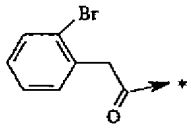
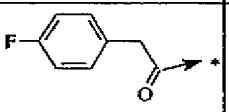
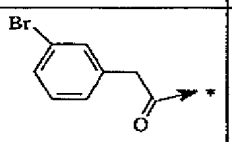
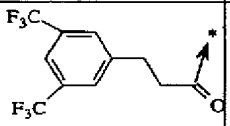
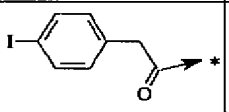
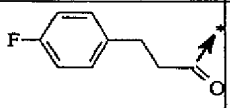
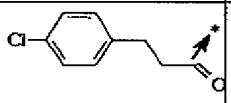
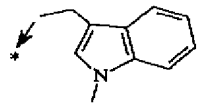
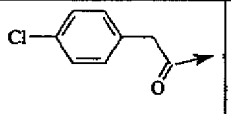
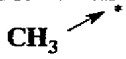
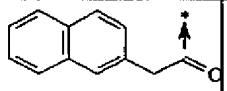
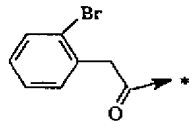
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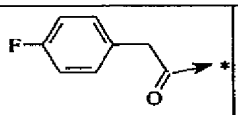
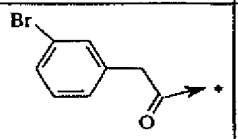
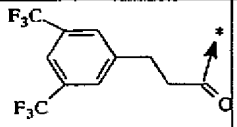
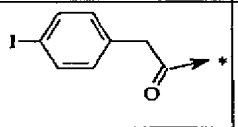
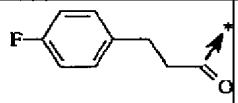
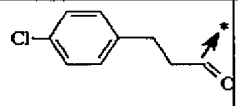
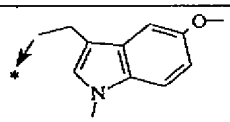
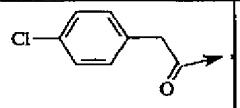
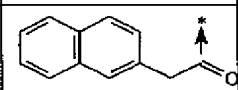
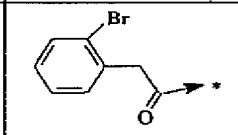
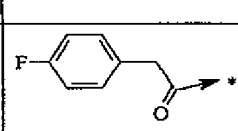
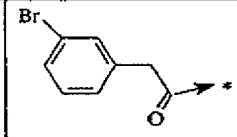
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656	"		"	98,4	5,34	519,2
657	"		"	95,4	5,16	501,3
658	"		"	89,8	5,08	485,3
659				80,76	4,84	410,2
660	"		"	61,69	4,97	426,2
661	"		"	90,93	4,79	454,1
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666	"		"	96,3	4,75	408,2
667	"		"	81,2	5,02	408,2
668			"	90,79	4,74	440,2
669	"		"	78,93	4,88	456,3
670	"		"	91,87	4,69	484,2
671	"		"	91,19	4,51	424,2
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673	"		"	89,5	5,46	542,2
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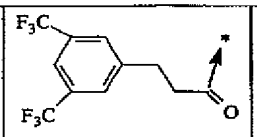
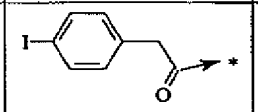
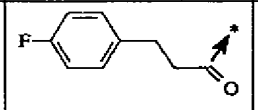
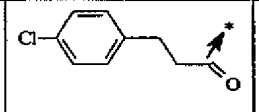
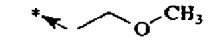
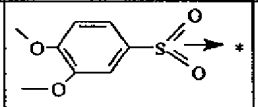
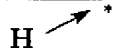
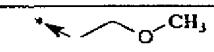
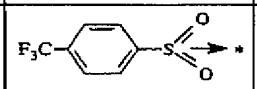
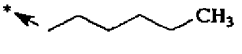
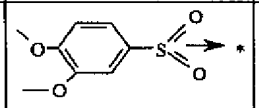
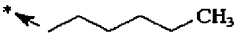
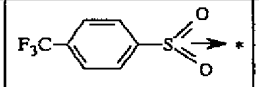
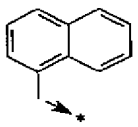
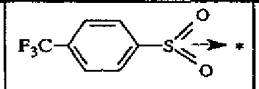
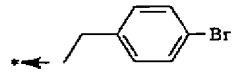
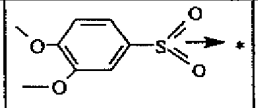
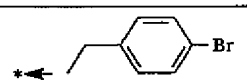
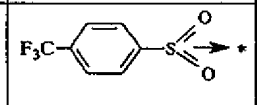
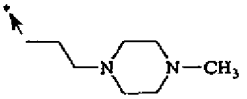
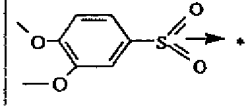
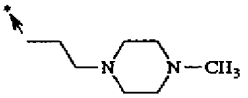
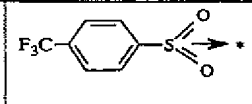
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683	"		"	94,79	5,16	516,1
684	"		"	96,5	4,9	422,3
685	"		"	88,2	5,19	438,2
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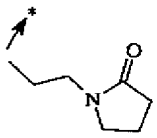
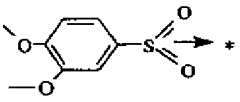
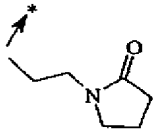
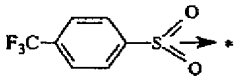
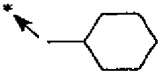
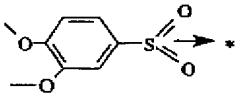
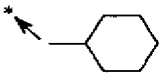
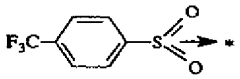
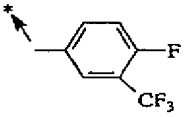
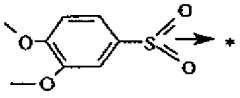
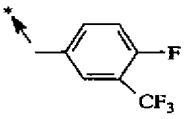
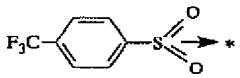
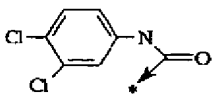
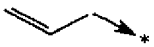
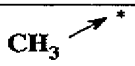
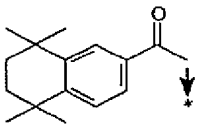
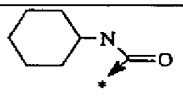
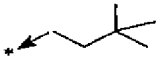
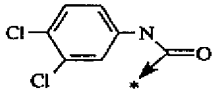
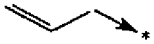
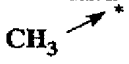
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692	"		"	95,24	5,05	516,3
693	"		"	96,6	4,8	422,2
694	"		"	90,4	5,04	438,2
695			"	93,12	4,78	454,2
696	"		"	86,11	4,92	470,3
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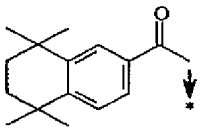
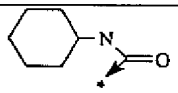
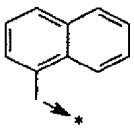
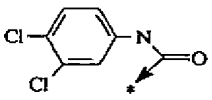
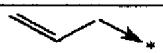
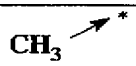
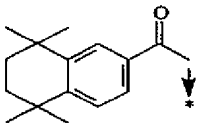
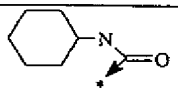
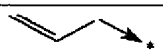
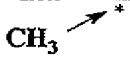
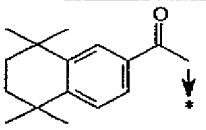
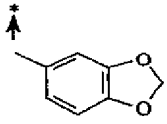
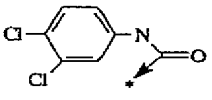
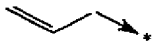
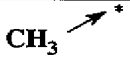
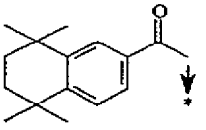
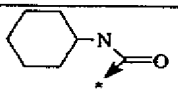
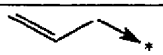
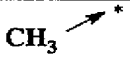
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703	"		"	85,6	4,96	468,2
704				78,36	3,14	359,1
705			"	47,4	3,9	367,1
706			"	69,72	4,28	385,2
707			"	34,86	4,96	393,2
708			"	37,54	4,91	449,2
709			"	81,57	4,46	483,1
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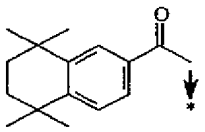
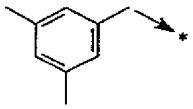
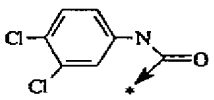
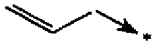
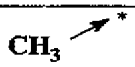
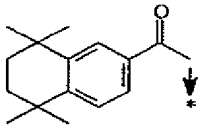
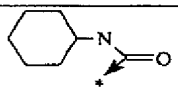
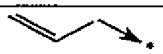
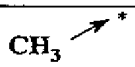
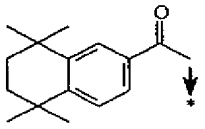
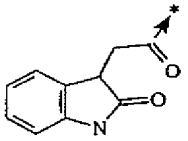
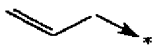
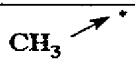
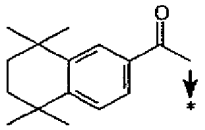
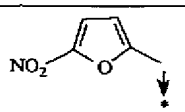
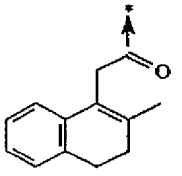
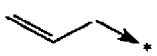
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714			"	74,98	3,84	434,2
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716			"	39,87	4,92	405,2
717			"	57,34	4,45	477,2
718			"	37,75	5,01	485,1
719				70,3	5,2	412,1
720	"	"		70,7	5,0	386,1
721	"	"		61,9	6,3	600,3
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723				65,0	5,1	412,2
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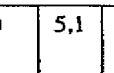
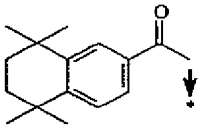
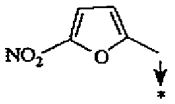
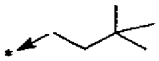
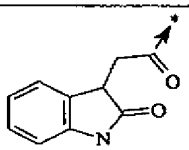
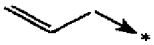
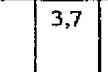
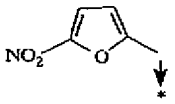
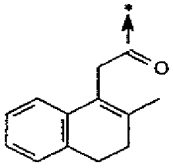
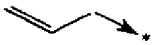
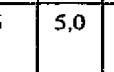
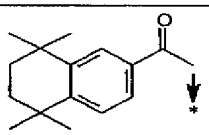
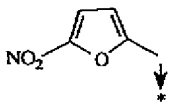
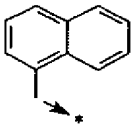
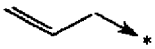
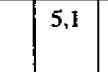
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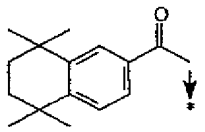
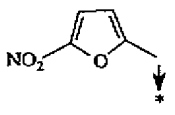
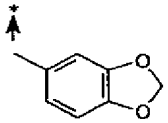
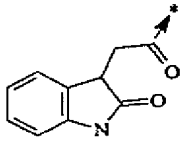
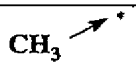
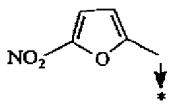
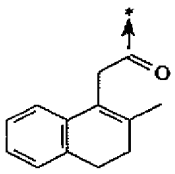
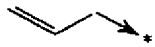
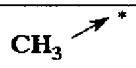
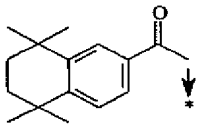
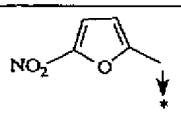
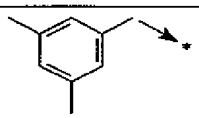
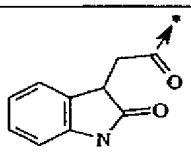
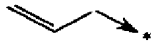
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729	"	"		82,3	6,2	656,3
730	"			93,8	4,7	406,3
731	"	"		80,7	4,6	380,3
732	"	"		84,1	5,9	594,3
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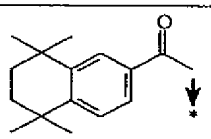
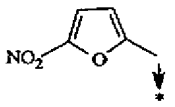
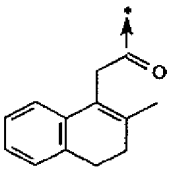
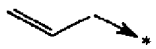
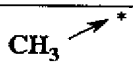
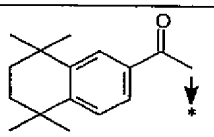
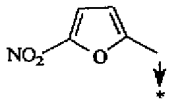
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744	"	"		65,1	5,9	572,4
745				80,0	4,0	398,3
746	"	"		76,9	3,8	372,3
747	"	"		42,7	5,8	586,4
748	"	"		64,6	4,4	483,3
749	"			87,4	5,3	409,3

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754	"	"		63,1	3,7	372,3
755	"	"		64,4	4,3	483,3
756	"			84,6	5,3	409,3
757	"	"		59,6	5,0	383,3
758	"	"		52,9	6,6	597,4
759	"	"		81,6	5,5	494,3
760		"		75,3	5,3	465,3
761	"	"		60,3	5,1	439,3

762	"	"		61,8	6,6	653,4
763	"	"		74,4	5,6	550,3
764				74,5	3,6	448,2
765	"	"		51,3	3,4	422,2
766	"	"		58,8	3,9	533,2
767	"			86,2	4,8	459,3
768	"	"		63,2	4,6	433,3
769	"	"		60,1	6,2	647,4
770	"	"		83,5	5,1	544,2
771				68,1	4,1	432,3
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773	"	"		41,1	5,8	620,4
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775	"			85,5	5,4	443,3
776	"	"		62,5	5,2	417,3
777	"	"		66,0	6,7	631,4
778	"	"		87,7	5,6	528,3

Etude pharmacologique

Les composés de la présente invention peuvent et ont été testés en ce qui concerne leur affinité pour différents sous-types de récepteurs de la somatostatine selon les procédures décrites ci-après.

Etude de l'affinité pour les sous-types de récepteurs de la somatostatine humaine :

L'affinité d'un composé de l'invention pour les sous-types de récepteurs de la somatostatine 1 à 5 (sst_1, sst_2, sst_3, sst_4 et sst_5, respectivement) est déterminée par la mesure de l'inhibition de la liaison de [^{125}I-Tyr^{11}]SRIF-14 à des cellules transfectées CHO-K1.

Le gène du récepteur sst_1 de la somatostatine humaine a été cloné sous forme d'un fragment génomique. Un segment *Pst*I-X*mn*I de 1,5 Kb contenant 100 pb de la région 5' non transcrite, 1,17 Kb de la région codante en totalité, et 230 bp de la région 3' non transcrite est modifié par l'addition du linker Bg1II. Le fragment d'ADN résultant est souscloné dans le site *BamH*I d'un pCMV-81 pour donner le plasmide d'expression chez les mammifères (fourni par Dr. Graeme Bell, Univ. Chicago). Une lignée de cellules clonées exprimant de façon stable le récepteur sst_1 est obtenue par transfection dans des cellules CHO-K1 (ATCC) grâce à la méthode de co-précipitation calcium phosphate. Le plasmide pRSV-neo (ATCC) est inclus comme marqueur de sélection. Des lignées de cellules clonées ont été sélectionnées dans un milieu RPMI 1640 contenant 0,5 mg/ml de G418 (Gibco), clonées en cercle, et multipliées en culture.

Le gène du récepteur sst_2 de la somatostatine humaine, isolé sous forme d'un fragment génomique d'ADN de 1,7 Kb *Bam*HI-*Hind*III et souscloné dans un vecteur plasmidique pGEM3Z (Promega), a été fourni par le Dr. G. Bell (Univ. of Chicago). Le vecteur d'expression des cellules de mammifères est construit en insérant le fragment *Bam*H1-*Hind*II de 1,7 Kb dans des sites de restriction endonucléase compatibles du plasmide pCMV5. Une lignée de cellules clonées est obtenue par transfection dans des cellules CHO-K1 grâce à la méthode de co-précipitation calcium phosphate. Le plasmide pRSV-neo est inclus comme marqueur de sélection.

Le récepteur sst_3 est isolé comme fragment génomique, et la séquence codante complète est contenue dans un fragment *Bam*HI/*Hind*III de 2,4 Kb. Le plasmide d'expression chez les mammifères, pCMV-h3, est construit par insertion du fragment *Nco*I-*Hind*III de 2,0 Kb dans le site EcoR1 du vecteur pCMV après modification des terminaisons et addition de linkers EcoR1. Une lignée de cellules clonées exprimant

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de façon stable le récepteur sst_3 est obtenue par transfection dans des cellules CHO-K1 (ATCC) par la méthode de co-précipitation au phosphate de calcium. Le plasmide pRSV-neo (ATCC) est inclus comme marqueur de sélection. Des lignées de cellules clonées ont été sélectionnées dans un milieu RPMI 1640 contenant 0,5 mg/ml de G418 (Gibco), clonées en cercle, et multipliées en culture.

Le plasmide d'expression du récepteur sst_4 humain, pCMV-HX, a été fourni par le Dr. Graeme Bell (Univ. Chicago). Ce vecteur contient le fragment génomique codant pour le récepteur sst4 humain de 1,4 Kb *Nhe*I-*Nhe*I, 456 pb de la région 5' non transcrite, et 200 pb de la région 3' non transcrite, cloné dans les sites *Xba*I/*Eco*R1 de PCMV-HX. Une lignée de cellules clonées exprimant de façon stable le récepteur sst_4 est obtenue par transfection dans des cellules CHO-K1 (ATCC) par la méthode de co-précipitation au phosphate de calcium. Le plasmide pRSV-neo (ATCC) est inclus comme marqueur de sélection. Des lignées de cellules clonées ont été sélectionnées dans un milieu RPMI 1640 contenant 0,5 mg/ml de G418 (Gibco), clonées en cercle, et multipliées en culture.

Le gène correpondant au récepteur sst_5 humain, obtenu par la méthode PCR en utilisant un clone génomique λ comme sonde, a été fourni par le Dr. Graeme Bell (Univ. Chicago). Le fragment PCR résultant de 1,2 Kb contient 21 paires de bases de la région 5' non transcrites, la région codante en totalité, et 55 pb de la région 3' non transcrite. Le clone est inséré dans un site EcoR1 du plasmide pBSSK(+). L'insert est récupéré sous la forme d'un fragment *Hind*III-*Xba*I de 1,2 Kb pour sousclonage dans un vecteur d'expression chez les mammifères, pCVM5. Une lignée de cellules clonées exprimant de façon stable le récepteur sst_5 est obtenue par transfection dans des cellules CHO-K1 (ATCC) par la méthode de co-précipitation au phosphate de calcium. Le plasmide pRSV-neo (ATCC) est inclus comme marqueur de sélection. Des lignées de cellules clonées ont été sélectionnées dans un milieu RPMI 1640 contenant 0,5 mg/ml de G418 (Gibco), clonées en cercle, et multipliées en culture.

Les cellules CHO-K1 exprimant de façon stable l'un des récepteurs sst humain sont cultivées dans un milieu RPMI 1640 contenant 10% de sérum foetal de veau et 0,4 mg/ml de généticine. Les cellules sont collectées avec de l'EDTA 0,5 mM et centrifugées à 500 g pendant environ 5 min à environ 4 °C. Le centrifugat est re-suspendu dans un milieu tampon 50 mM Tris à pH 7,4 et centrifugé deux fois à 500 g pendant environ 5 min à environ 4 °C. Les cellules sont lysées par sonication et centrifugées à 39000 g pendant environ 10 min à 4 °C. Le centrifugat est re-suspendu

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dans le même milieu tampon et centrifugé at 50000 g pendant 10 min à environ 4 °C et les membranes dans le centrifugat obtenu sont stockées à - 80 °C.

Des tests d'inhibition compétitive de liaison avec [^{125}I-Tyr^{11}]SRIF-14 sont effectués en double à l'aide de plaques en polypropylène de 96 puits. Les membranes cellulaires (10 μg protéine/puits) sont incubées avec [^{125}I-Tyr^{11}]SRIF-14 (0,05 nM) pendant environ 60 min à environ 37 °C dans un milieu tampon 50 mM HEPES (pH 7,4) comprenant 0,2% BSA, 5 mM de $MgCl_2$, 200 KIU/ml de Trasylol, 0,02 mg/ml de bacitracine et 0,02 mg/ml de fluorure de phénylméthylsulphonyle.

La [^{125}I-Tyr^{11}]SRIF-14 liée est séparée de la [^{125}I-Tyr^{11}]SRIF-14 libre par filtration immédiate à travers des plaques filtres en fibre de verre GF/C (Unifilter, Packard) préimprégné avec 0,1 % de polyéthylènimine (P.E.I.), en utilisant un Filtermate 196 (Packard). Les filtres sont lavés avec du tampon 50 mM HEPES à environ 0-4 °C pendant environ 4 secondes et leur radioactivité est déterminée à l'aide d'un compteur (Packard Top Count).

La liaison spécifique est obtenue en soustrayant la liaison non spécifique (déterminée en présence de 0,1 μM SRIF-14) de la liaison totale. Les données relatives à la liaison sont analysées par analyse en régression non-linéaire assistée par ordinateur (MDL) et les valeurs des constantes d'inhibition (Ki) values sont déterminées.

La détermination du caractère agoniste ou antagoniste d'un composé de la présente invention est effectuée à l'aide du test décrit ci-après.

Test fonctionnel : Inhibition de la production d'AMPc intracellulaire :

Des cellules CHO-K1 exprimant les sous-types de récepteurs de la somatostatine humaine (SRIF-14) sont cultivées dans des plaques à 24 puits dans un milieu RPMI 1640 avec 10% de sérum foetal de veau et 0,4 mg/ml de généticine. Le milieu est changé le jour précédant l'expérience.

Les cellules à raison de 10^5 cellules/puits sont lavées 2 fois avec 0,5 ml de nouveau milieu RPMI comprenant 0,2 % BSA complété par 0,5 mM de 3-isobutyl-1-méthylxanthine (IBMX) et incubées pendant environ 5 min à environ 37 °C.

. la production d'AMP cyclique est stimulée par l'addition de 1 mM de forskoline (FSK) pendant 15-30 minutes à environ 37 °C.

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. l'effet inhibiteur de la somatostatine d'un composé agoniste est mesuré par l'addition simultanée de FSK (1µM) , SRIF-14 (10^{-12} M to 10^{-6} M) et du composé à tester (10^{-10} M à 10^{-5} M).

. l'effet antagoniste d'un composé est mesuré par l'addition simultanée de FSK (1µM), SRIF-14 (1 to 10 nM) et du composé à tester (10^{-10} M to 10^{-5} M).

Le milieu réactionnel est éliminé et 200 ml de HCl 0,1 N sont ajoutés. La quantité d'AMPc est mesurée par un test radioimmunologique (Kit FlashPlate SMP001A, New England Nuclear).

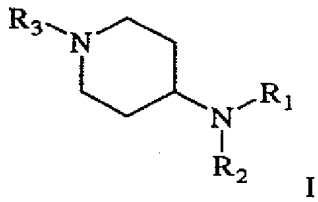
Résultats :

Les tests effectués selon les protocoles décrits ci-dessus ont permis de montrer que les produits de formule générale (I) définie dans la présente demande ont une bonne affinité pour au moins l'un des sous-types de récepteurs de la somatostatine, la constante d'inhibition K_i étant inférieure au micromolaire pour certains des composés exemplifiés.

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Revendications

1. Composés de formule générale



I

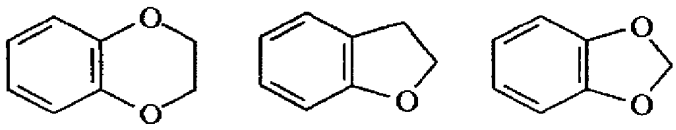
sous forme racémique, d'énantiomère ou toutes combinaisons de ces formes, dans laquelle :

R_1 représente un radical $(C_1\text{-}C_{16})$alkyle linéaire ou ramifié, alkényle, alkynyle, $-(CH_2)_m\text{-}Y\text{-}Z_{11}$ ou $-(CH_2)_m\text{-}Z_{12}$ dans lequel

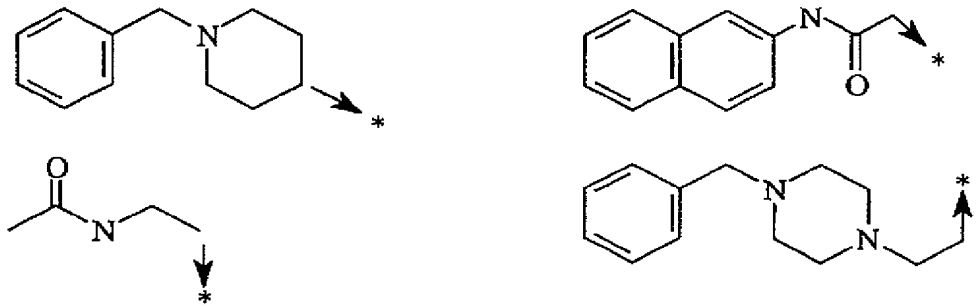
Z_{11} représente un $(C_1\text{-}C_6)$alkyle ou aryle éventuellement substitué,

Z_{12} représente cyano, cyclohexényle, *bis*-phényle, $(C_3\text{-}C_7)$cycloalkyle, $(C_3\text{-}C_7)$hétérocycloalkyle éventuellement substitué, aryle éventuellement substitué ou hétéroaryle éventuellement substitué,

ou bien Z_{12} représente un radical de formule



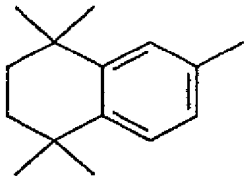
ou bien R_1 représente un radical de formule

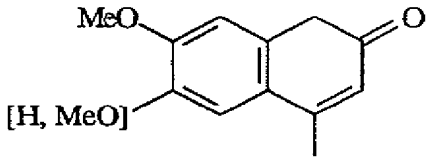


R_2 représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 ;

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R_3 représente l'atome d'hydrogène, un radical alkyle éventuellement substitué, alkényle, alkynyle, aralkyle éventuellement susbtitué, hétéroarylalkyle éventuellement substitué, ou un radical de formule $-C(Y)-NHX_1$, $-(CH_2)_u-C(O)X_2$, SO_2X_3 ou



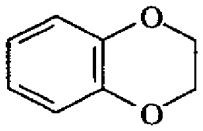


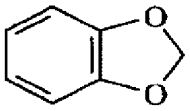
X_1 représente un radical (C_1-C_{15})alkyle linéaire ou ramifié, alkényle, alkynyle, $-(CH_2)_m-Y-Z_{21}$ ou $-(CH_2)_pZ_{22}$ dans lequel

Z_{21} représente un (C_1-C_6)alkyle

Z_{22} représente cyclohexényle, indanyle, *bis*-phényle, (C_3-C_7)cycloalkyle, (C_3-C_7)hétérocycloalkyle, mono- ou di-alkylamino, -C(O)-O-alkyle, ou aryle ou hétéroaryle éventuellement substitué,

ou Z_{22} représente un radical de formule



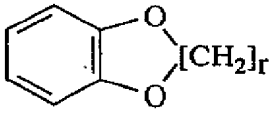


X_2 représente un radical (C_1-C_{10})alkyle linéaire ou ramifié, alkényle éventuellement substitué par un radical phényle (le radical phényle étant lui-même éventuellement substitué), alkynyle, ou un radical de formule $-(CH_2)_m-W-(CH_2)_q-Z_{23}$ ou $-(CH_2)_p-U-Z_{24}$ dans lequel

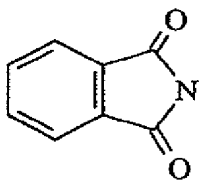
Z_{23} représente un (C_1-C_6)alkyle ou aryle éventuellement substitué ;

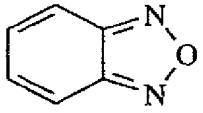
Z_{24} représente alkyle, cyclohexényle, *bis*-phényle, (C_3-C_7)cycloalkyle éventuellement substitué, (C_3-C_7)hétérocycloalkyle, cyano, amino, mono ou di-alkylamino, ou aryle ou hétéroaryle éventuellement substitué,

ou Z_{24} représente un radical de formule

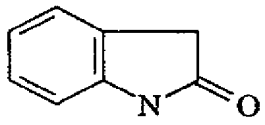
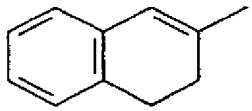


r = 1,2 ou 3

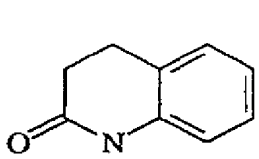
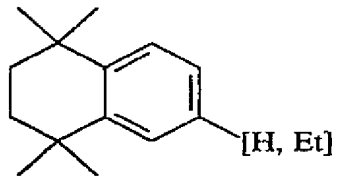


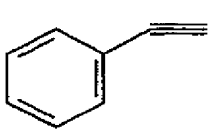
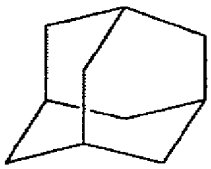
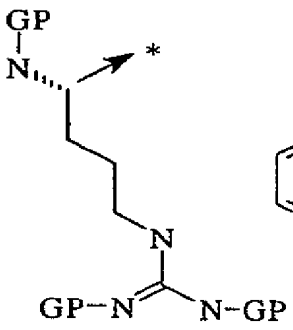


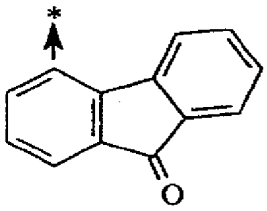
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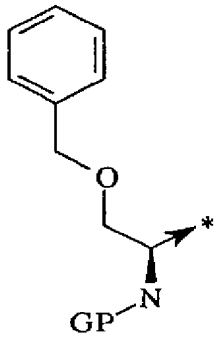



ou bien X_2 représente un radical représenté ci-dessous :

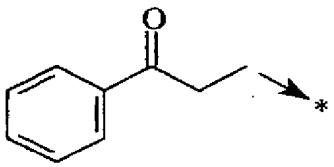



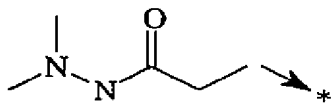




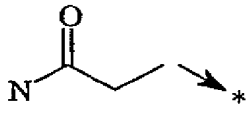


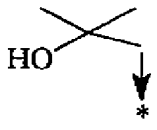


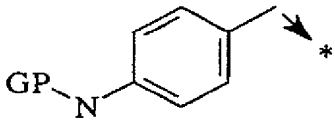
5

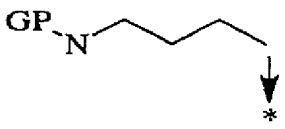


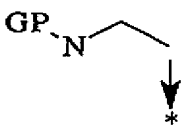


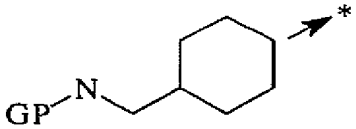












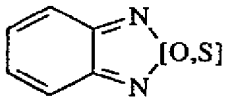
où le groupe protecteur (GP) représente H ou le *tert*-butyloxycarbonyle ;

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X_3 représente un radical (C_1-C_{10})alkyle linéaire ou ramifié, alkényle éventuellement substitué par un radical phényle (le radical phényle étant lui-même éventuellement substitué), CF_3, ou $-(CH_2)_pZ_{25}$ dans lequel

Z_{25} représente aryle ou hétéroaryle éventuellement substitué,

ou bien X_3 représente un radical de formule



éventuellement substitué par un ou plusieurs radicaux halo identiques ou différents ;

Y représente un atome d'oxygène ou de soufre ;

W représente un atome d'oxygène, de soufre ou SO_2 ;

U représente une liaison covalente ou l'atome d'oxygène ;

n est un entier de 0 à 4 ;

m est un entier de 1 à 6 ;

p est un entier de 0 à 6 ;

q est un entier de 0 à 2,

ou leurs sels d'addition avec les acides minéraux ou organiques pharmaceutiquement acceptables.

2. Composés de formule générale I telle que définie à la revendication 1, caractérisée en ce que

i) le ou les substituant(s) que peuvent porter les radicaux aryle que représentent Z_{11} et Z_{12} et hétéroaryle que représente Z_{12} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, $-CF_3$, $-OCF_3$, phényle, phénoxy, aminosulfonyle ;

ii) le ou les substituant(s) que peut porter le radical hétérocycloalkyle que représente Z_{12} sont choisis indépendamment parmi les radicaux oxy et alkyle ;

iii) le ou les substituant(s) que peut porter les radicaux aryle et hétéroaryle que représente Z_{22} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkényle, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, aminosulfonyle, pipéridinosulfonyle, mono- ou di-alkylamino, -C(O)-O-alkyle, -C(O)–alkyle, ou phényle, phénoxy, phénylthio, benzyloxy, le radical phényle pouvant être substitué ;

iv) le ou les substituant(s) que peut porter les radicaux aryle que représente Z_{23} et Z_{24}, cycloalkyle et hétéroaryle que représente Z_{24} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3, OCF_3, $OCHF_2$, SCF_3, nitro, cyano, azido, hydroxy, -C(O)O-alkyle, -O-C(O)-alkyle, -NH-C(O)-alkyle, alkylsulfonyle, mono- ou di-alkylamino, amino, aminoalkyle, pyrrolyle, pyrrolydinyle ou bien les radicaux phényle, phénoxy, phénylthio, benzyle, benzyloxy dont le radical aryle est éventuellement substitué par un ou plusieurs radicaux alkyle, CF_3 ou halo ;

v) le ou les substituant(s) que peut porter les radicaux aryle et hétéroaryle que représente Z_{25} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3, OCF_3, nitro, cyano, -NH-C(O)-alkyle, alkylsulfonyle, amino, mono- et di-alkylamino, phényle, pyridino ;

vi) le substituant que peut porter le radical alkyle que représente R_3 est le radical cyano.

vii) le ou les substituant(s) que peut porter le radical aralkyle que représente R_3 sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3, OCF_3, $OCHF_2$, SCF_3, $SCHF_2$, nitro, cyano, -C(O)O-alkyle, alkylsulfonyle, thiadiazolyle, ou bien les radicaux phényle et phénoxy dont le radical phényle est éventuellement substitué par un ou plusieurs radicaux halo.

viii) le ou les substituant(s) que peut porter le radical hétéroarylalkyle que représente R_3 sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo ou nitro.

3. Composés de formule générale I telle que définie à l'une des revendications 1 à 2, caractérisée en ce que

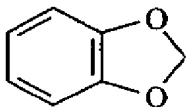
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R_1 représente un radical $(C_1\text{-}C_6)$alkyle linéaire ou ramifié, le radical $-(CH_2)_m\text{-}Y\text{-}Z_{11}$ ou $-(CH_2)_m\text{-}Z_{12}$ dans lequel

Z_{11} représente un $(C_1\text{-}C_6)$alkyle,

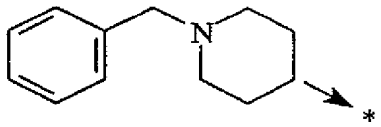
Z_{12} représente *bis*-phényle, $(C_3\text{-}C_7)$cycloalkyle, $(C_3\text{-}C_7)$hétérocycloalkyle éventuellement substitué, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy,

ou bien Z_{12} représente



Y représente l'atome d'oxygène,

ou bien R_1 représente un radical de formule

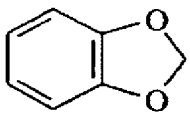


R_2 représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical $(C_1\text{-}C_{15})$alkyle linéaire ou ramifié, ou $-(CH_2)_pZ_{22}$ dans lequel

Z_{22} représente cyclohexényle, *bis*-phényle, $(C_3\text{-}C_7)$cycloalkyle, $(C_3\text{-}C_7)$hétérocycloalkyle, mono- ou di-alkylamino, -C(O)-O-alkyle, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, pipéridinosulfonyle, $-C(O)$-O-alkyle, -C(O)-alkyle, ou phényle,

ou bien Z_{22} représente un radical de formule



X_2 représente un radical $(C_1\text{-}C_{10})$alkyle linéaire ou ramifié, alkynyle, $-(CH_2)_m\text{-}W\text{-}(CH_2)_q\text{-}Z_{23}$ ou $-(CH_2)_p\text{-}U\text{-}Z_{24}$ dans lequel

W représente SO_2,

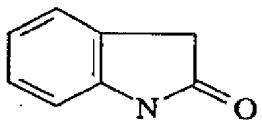
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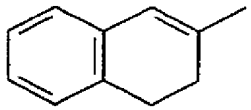
U représente une liaison covalente,

Z_{23} représente un radical aryle ;

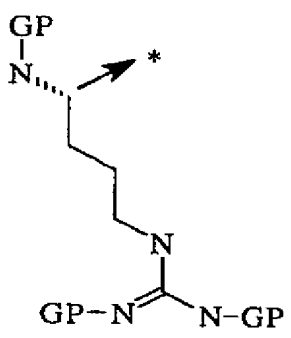
Z_{24} représente cyclohexényle, *bis*-phényle, (C_3-C_7)cycloalkyle éventuellement substitué par un radical aminoalkyle, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo, alkyle, alkoxy, -CF_3, -OCF_3, SCF_3, hydroxy, -O-C(O)-alkyle, mono- ou di-alkylamino, amino

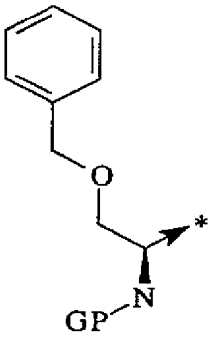
ou Z_{24} représente un radical de formule





ou bien X_2 représente





X_3 représente un radical $-(CH_2)_pZ_{25}$ dans lequel Z_{25} représente un radical aryle éventuellement substitué par un ou plusieurs radicaux identiques ou différents choisis parmi alkoxy et CF_3,

R_3 représente l'atome d'hydrogène, un radical alkyle, alkényle, hétéroarylalkyle éventuellement substitué ou un radical de formule $-C(Y)-NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical $-(CH_2)_pZ_{22}$ dans lequel

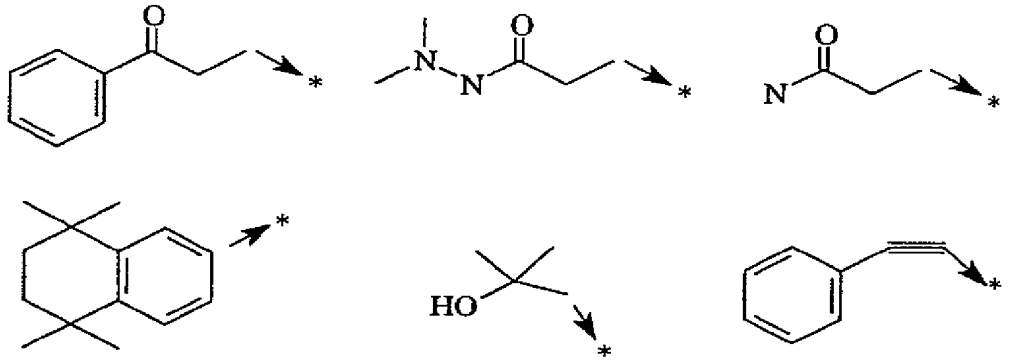
Z_{22} représente un radical aryle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3, nitro, phénoxy ;

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X_2 représente le radical vinyle substitué par un phényle, le radical phényle étant lui-même éventuellement substitué par un ou plusieurs radicaux halo, ou $-(CH_2)_p$-U-Z_{24} dans lequel

Z_{24} représente alkyle, (C_3-C_7)cycloalkyle, (C_3-C_7)hétérocycloalkyle, *bis*-phényle, amino, mono ou di-alkylamino, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis parmi alkoxy, bromo, chloro, fluoro, hydroxy, CF_3, nitro, amino, mono- et di-alkylamino, pyrrolyle,

ou bien X_2 représente un radical de formule



X_3 représente un radical (C_1-C_{10})alkyle linéaire ou ramifié, le radical vinyle substitué par un radical (le radical phényle étant lui-même éventuellement substitué), CF_3, ou $-(CH_2)_pZ_{25}$ dans lequel

Z_{25} représente aryle ou hétéroaryle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3, nitro, -NH-C(O)-alkyle, mono- et di-alkylamino.

4. Composés de formule I telle que définie à l'une des revendications 1 à 3, caractérisée en ce que

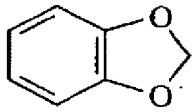
R_1 représente un radical (C_1-C_6)alkyle linéaire ou ramifié, le radical $-(CH_2)_m$-Y-Z_{11} ou $-(CH_2)_m$-Z_{12} dans lequel

Z_{11} représente un (C_1-C_6)alkyle,

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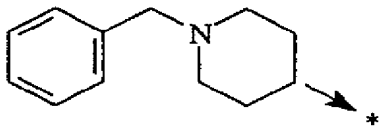
Z_{12} représente naphtyle, morpholino, *bis*-phénylc, pyrrolidinyle substitué par le radical oxy, ou bien les radicaux phényle, pipérazinyle, pyridinyle et indolyle qui sont éventuellement substitués par un ou plusieurs substituants choisis indépendamment parmi les radicaux bromo, fluoro, chloro, alkyle, alkoxy, $-CF_3$, $-OCF_3$;

ou bien Z_{12} représente



Y représente l'atome d'oxygène,

ou bien R_1 représente un radical de formule :

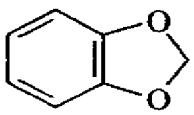


R_2 représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical $(C_1\text{-}C_{10})$alkyle linéaire ou ramifié, ou $-(CH_2)_pZ_{22}$ dans lequel

Z_{22} représente cyclohexyle, cyclohexényle, *bis*-phényle, morpholino, pipéridino, mono- ou di-alkylamino, -C(O)-O-alkyle, ou phényle, naphtyle ou furyle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3, OCF_3, nitro, cyano, azido, pipéridinosulfonyle, –C(O)-O-alkyle, -C(O)-alkyle ou phényle,

ou bien Z_{22} représente un radical de formule



X_2 représente un radical alkyle, alkynyle, $-(CH_2)_m\text{-}W\text{-}(CH_2)_q\text{-}Z_{23}$ ou $-(CH_2)_pZ_{24}$ dans lequel

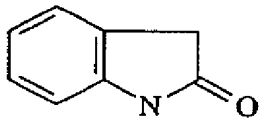
W représente SO_2 ;

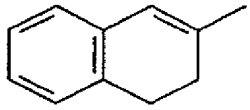
Z_{23} représente le radical phényle ;

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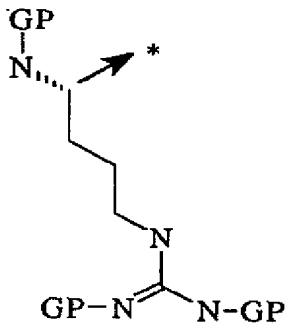
Z_{24} représente cyclohexényle, *bis*-phényle, cyclohexyle éventuellement substitué par un radical aminoalkyle, ou phényle, naphtyle, benzothiényle, thiényle ou indolyle éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo, alkyle, alkoxy, $-CF_3$, $-OCF_3$, SCF_3, hydroxy, -O-C(O)-alkyle, -NH-C(O)-alkyle, mono- ou di-alkylamino, amino, ou

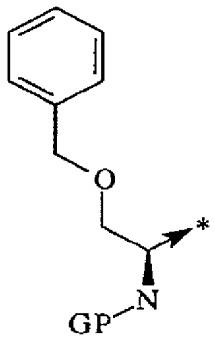
Z_{24} représente un radical de formule





ou bien X_2 représente





X_3 représente un radical $-(CH_2)_pZ_{25}$ dans lequel Z_{25} représente le radical phényle éventuellement substitué par un ou plusieurs radicaux identiques ou différents choisis parmie alkoxy et CF_3 ,

R_3 représente l'atome d'hydrogène, un radical alkyle, alkényle ou furyl-méthyl susbtitué par un ou plusieurs radicaux nitro, ou un radical de formule $-C(Y)-NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

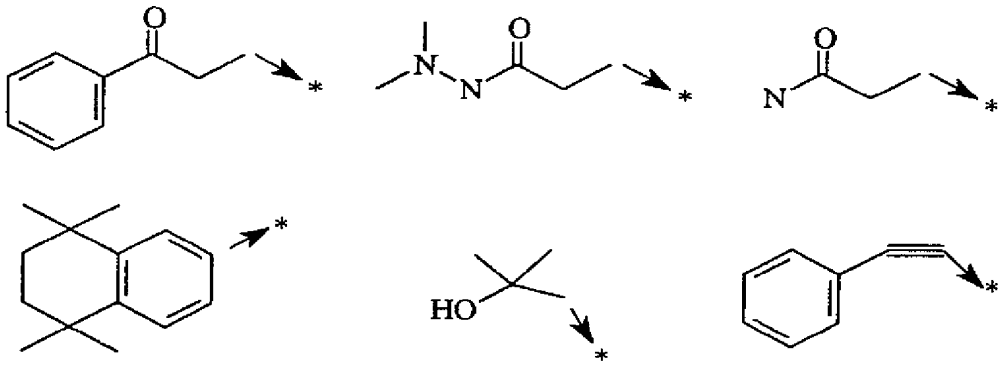
X_1 représente un radical $-(CH_2)_pZ_{22}$ dans lequel

Z_{22} représente le radical phényle ou naphtyle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3, nitro, phénoxy,

X_2 représente le radical vinyle substitué par un radical phényle lui-même éventuellement substitué par un ou plusieurs radicaux halo, ou $-(CH_2)_p$-U-Z_{24} dans lequel

Z_{24} représente alkyle, cyclohexyle, tétrahydrofuryle, *bis*-phényle, amino, mono ou di-alkylamino, ou phényle, indolyle, thiényle, pyridinyle, benzothiényle et furyle éventuellement substitué par un ou plusieurs radicaux choisis parmi alkoxy, bromo, chloro, fluoro, amino, mono- et di-alkylamino, nitro, hydroxy, pyrrolyle

ou bien X_2 représente un radical de formule



X_3 représente un radical (C_1-C_{10})alkyle linéaire ou ramifié, le radical vinyle substitué par un radical phényle, CF_3, ou $-(CH_2)_pZ_{25}$ dans lequel

Z_{25} représente un radical phényle, napthyle, thiényle, pyrazolyle ou thiazolyle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3, nitro, -NH-C(O)-alkyle, mono- et di-alkylamino ;

5. Composés de formule I telle que définie à l'une des revendications 1 à 4, caractérisée en ce que R_1 représente le radical $-(CH_2)_mZ_{12}$ dans lequel m = 2 et Z_{12} représente *bis*-phényle ou bien le radical indolyle substitués par un ou plusieurs substituants choisis indépendamment parmi les radicaux alkyle et alkoxy.

6. Composés de formule I telle que définie à l'une des revendications 1 à 5, caractérisée en ce que R_2 représente les radicaux de formule $-C(Y)NHX_1$ et $-C(O)X_2$ dans laquelle

Y représente S ;

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X_1 représente un radical phényle éventuellement substitué par un ou plusieurs radicaux azido,

X_2 représente $-(CH_2)_pZ_{24}$ dans lequel

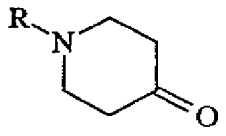
p est égal à 1, 2 ou 3,

Z_{24} représente cyclohexyle, ou phényle ou benzothiényle éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo ou $-CF_3$.

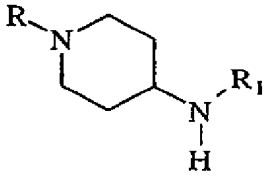
7. Composés de formule I telle que définie à l'une des revendications 1 à 6, caractérisée en ce que R_3 représente l'atome d'hydrogène ou le radical méthyle.

8. Procédé de préparation, en phase liquide, de composés de formule I telle que définie à la revendication 1, caractérisé en ce qu'il comprend

l'amination réductrice de la pipéridone N-substituée suivante



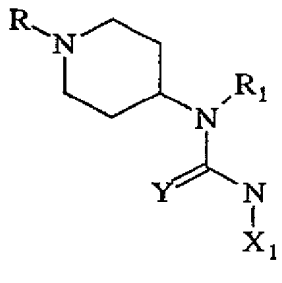
dans laquelle R représente le radical méthyle ou Boc, en présence d'une amine de formule R_1NH_2 dans laquelle R_1 a la signification indiquée à la revendication 1, pour obtenir le composé de formule 1



(1)

composé de formule (1) que l'on fait réagir avec

A) soit un composé de formule $X_1NC(Y)$ dans laquelle X_1 et Y ont la signification indiquée à la revendication 1, pour obtenir un composé de formule (2)

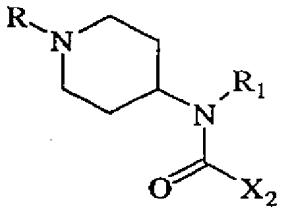


(2)

composé de formule (2) qui représente le composé de formule (I) correspondant dans lequel R_3 représente Me ou Boc et qui, lorsque R_3 représente Boc, peut être soumis à un traitement acide pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

composé de formule (I) ainsi obtenu que l'on peut faire réagir avec un composé de formule $X_1NC(Y)$, X_2CO_2H ou bien X_3SO_2Cl dans laquelle X_1, Y, X_2 et X_3 ont la signification indiquée à la revendication 1, pour obtenir le composé de formule I correspondant dans laquelle R_2 représente un radical de formule $-C(Y)NHX_1$ et R_3 le radical$-C(Y)-NHX_1$, $-C(O)X_2$ ou SO_2X_3 respectivement ;

B) soit un composé de formule X_2CO_2H dans laquelle X_2 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (3)



(3)

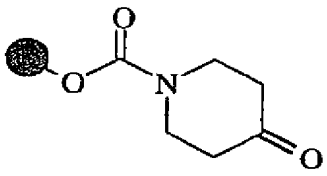
composé de formule (3) qui représente le composé de formule (I) correspondant dans lequel R_3 représente Me ou Boc et qui, lorsque R_3 représente Boc, peut être soumis à un traitement acide pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

composé de formule (I) ainsi obtenu que l'on peut faire réagir avec un composé de formule $X_1NC(Y)$, X_2CO_2H ou bien X_3SO_2Cl dans laquelle X_1, Y, X_2 et X_3 ont la signification indiquée à la revendication 1, pour obtenir le composé de formule I correspondant dans laquelle R_2 représente un radical de formule $-C(O)X_2$ et R_3 le radical$-C(Y)-NHX_1$, $-C(O)X_2$ ou SO_2X_3 respectivement.

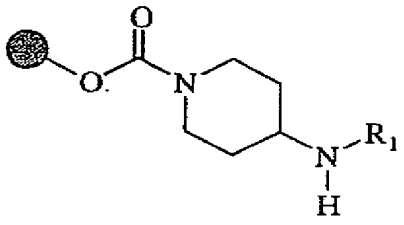
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9. Procédé de préparation, en phase solide, de composés de formule I telle que définie à la revendication 1, caractérisé en ce qu'il comprend

l'amination réductrice de la résine cétonique



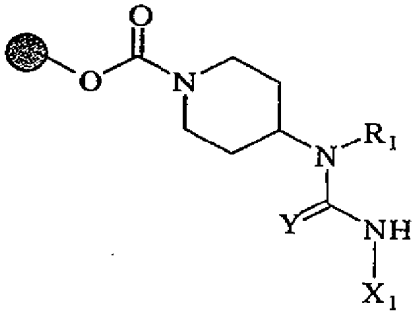
en présence d'une amine de formule R_1NH_2 dans laquelle R_1 a la signification indiquée à la revendication 1, pour obtenir le composé de formule (4)



(4)

composé de formule (4) que l'on fait réagir avec

A) soit un composé de formule $X_1NC(Y)$ dans laquelle X_1 et Y ont la signification indiquée à la revendication 1, pour obtenir un composé de formule (5)

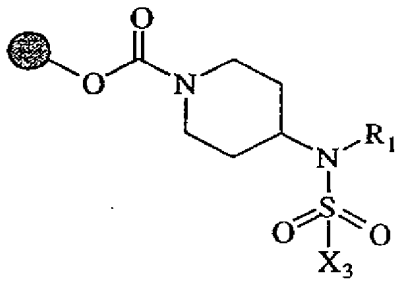


(5)

suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

B) soit un composé de formule X_3SO_2Cl dans laquelle X_3 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (6)

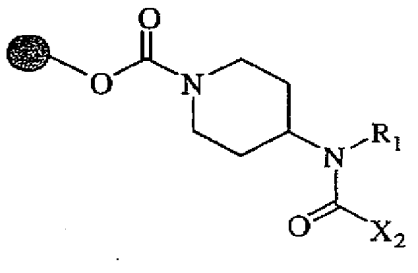
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(6)

suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

C) soit un composé de formule X_2CO_2Cl dans laquelle X_2 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (7)



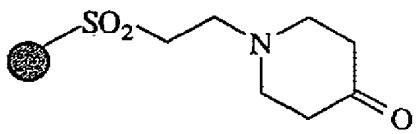
(7)

suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène ;

D) soit un composé de formule X_2CO_2H dans laquelle X_2 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (7) tel que défini ci-dessus, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène.

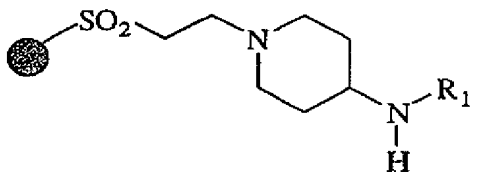
10. Procédé de préparation, en phase solide, de composés de formule I telle que définie à la revendication 1, caractérisé en ce qu'il comprend

l'amination réductrice de la résine cétonique



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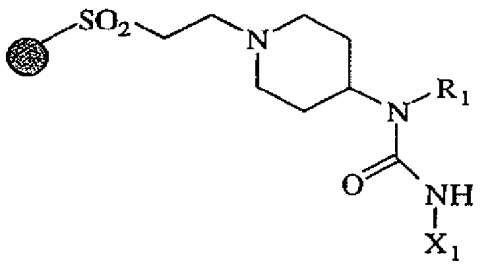
en présence d'une amine de formule R_1NH_2 dans laquelle R_1 a la signification indiquée à la revendication 1, pour obtenir le composé de formule (8)



(8)

composé de formule (8) que l'on fait réagir avec

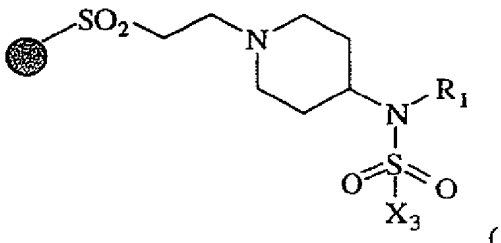
A) soit un composé de formule $X_1NC(O)$ dans laquelle X_1 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (9)



(9)

composé (9) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini à la revendication 1 et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant ;

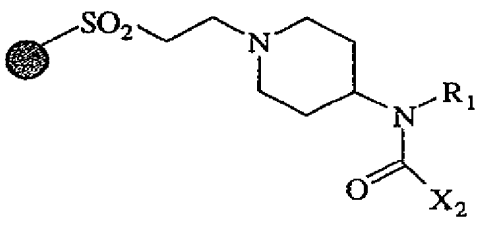
B) soit un composé de formule X_3SO_2Cl dans laquelle X_3 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (10)



(10)

composé (10) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini à la revendication 1 et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant ;

C) soit un composé de formule X_2CO_2Cl dans laquelle X_2 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (11)



(11)

composé (11) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini à la revendication 1 et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant ;

D) soit un composé de formule X_2CO_2H dans laquelle X_2 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (11) tel que défini ci-dessus,

composé (11) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini à la revendication 1 et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant.

11. A titre de médicaments, les produits de formule I telle que à l'une des revendications 1 à 7, ainsi que les sels d'addition avec les acides minéraux ou organiques pharmaceutiquement acceptables desdits produits de formule I.

12. Compositions pharmaceutiques contenant, à titre de principe actif, un au moins des médicaments tels que définis à la revendication 11, en association avec un support pharmaceutiquement acceptable.

13. Utilisation d'un composé de formule I telle que définie à l'une des revendications 1 à 7 pour la préparation d'un médicament destiné à traiter les états pathologiques ou les maladies dans lesquels un (ou plusieurs) des récepteurs de la somatostatine est(sont) impliqué(s).

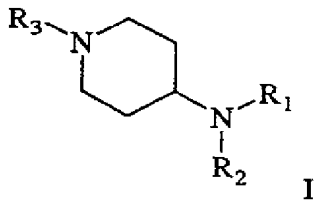
14. Utilisation selon la revendication 13 pour la préparation d'un médicament destiné à traiter l'acromégalie, des adénomes hypophysaires ou des tumeurs gastroentéropancréatiques endocriniennes dont le syndrome carcinoïde.

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Abrégé

La présente demande a pour objet de nouveaux dérivés de 4-aminopipéridines de formule



I

dans laquelle R_1, R_2 et R_3 représentent divers groupes variables, leurs procédés de préparation par des méthodes de synthèse en parallèle en phase liquide et solide. Ces produits ayant une bonne affinité avec certains sous-types de récepteurs de la somatostatine, ils sont particulièrement intéressants pour traiter les états pathologiques ou les maladies dans lesquels un (ou plusieurs) des récepteurs de la somatostatine est (sont) impliqué(s).

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RÉPUBLIQUE FRANÇAISE

INPI
INSTITUT NATIONAL DE LA PROPRIETE INDUSTRIELLE

RAPPORT DE RECHERCHE PRÉLIMINAIRE

établi sur la base des dernières revendications déposées avant le commencement de la recherche

2802206

N° d'enregistrement national

FA 590678
FR 9915724

DOCUMENTS CONSIDÉRÉS COMME PERTINENTS		Revendication(s) concernée(s)	Classement attribué à l'invention par l'INPI
Catégorie	Citation du document avec indication, en cas de besoin, des parties pertinentes		
A	WO 99 22735 A (PASTERNAK ALEXANDER ;PATCHETT ARTHUR A (US); GUO LIANGQUIN (US); Y) 14 mai 1999 (1999-05-14) * revendications 1,5-14; exemples *	1,11-14	C07D417/14 C07D409/14 C07D401/12 C07D413/12 C07D211/58 A61K31/435 A61P5/08 A61P5/02 A61P5/48 A61P35/00
A	WO 98 44921 A (PASTERNAK ALEXANDER ;PATCHETT ARTHUR A (US); YANG LIHU (US); BERK) 15 octobre 1998 (1998-10-15) * revendications 1,21-35; exemples *	1,11-14	
A	DE 27 51 138 A (ANPHAR SA) 24 mai 1978 (1978-05-24) * page 25 - page 27; revendications 1,35 *	1,11-14	
A	DE 25 30 894 A (PFIZER) 5 février 1976 (1976-02-05) * exemples 10,17,29,33 *	1,11-14	

DOMAINES TECHNIQUES RECHERCHÉS (Int.Cl.7)

C07D
A61P
A61K

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Date d'achèvement de la recherche	Examinateur
19 octobre 2000	Bosma, P

CATÉGORIE DES DOCUMENTS CITÉS

X : particulièrement pertinent à lui seul
Y : particulièrement pertinent en combinaison avec un autre document de la même catégorie
A : arrière-plan technologique
O : divulgation non-écrite
P : document intercalaire

T : théorie ou principe à la base de l'invention
E : document de brevet bénéficiant d'une date antérieure à la date de dépôt et qui n'a été publié qu'à cette date de dépôt ou qu'à une date postérieure.
D : cité dans la demande
L : cité pour d'autres raisons

& : membre de la même famille, document correspondant

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